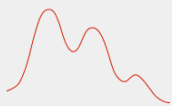
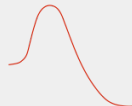


7.5: SN1 vs SN2

7.5.1 Comparison Between S_N1 and S_N2 Reactions

Till now, we have finished the basic concepts about S_N1 and S_N2 reactions. You probably already noticed that the two type of reactions have some similarities, also quite different though. It will be very helpful to put them together for comparison. To help you get in-depth understanding of the two types of mechanism, it is highly recommended that you have a summary in your own way. The following comparison is provided here for your reference.

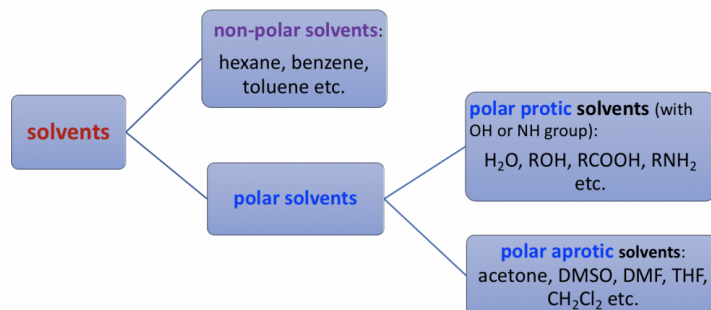
	S _N 1	S _N 2
Rate law	Rate = $k[\text{electrophile}]$	Rate = $k[\text{nucleophile}] \times [\text{electrophile}]$
Mechanism	multiple steps with carbocation intermediate	one step, concerted
Reaction Diagram		
Stereochemistry	racemization on reaction center	inversion on reaction center
Electrophilic Substrate	tertiary 3° > secondary 2° > primary 1° and methyl	primary 1° and methyl > secondary 2° > tertiary 3°
Nucleophile	weak nucleophile, solvolysis	strong nucleophile

7.5.2 Solvent Effect on S_N1 and S_N2 Reactions

Other than the factors we have talked about so far, solvent is another key factor that affect nucleophilic substitution reactions. Proper solvent is required to facilitate a certain mechanism. For some cases, picking up the appropriate solvent is the effective way to control which pathway the reaction proceed.

To understand the solvent effect, we first of all need to have more detailed discussions about solvents, then learn how to choose good solvent for a specific reaction.

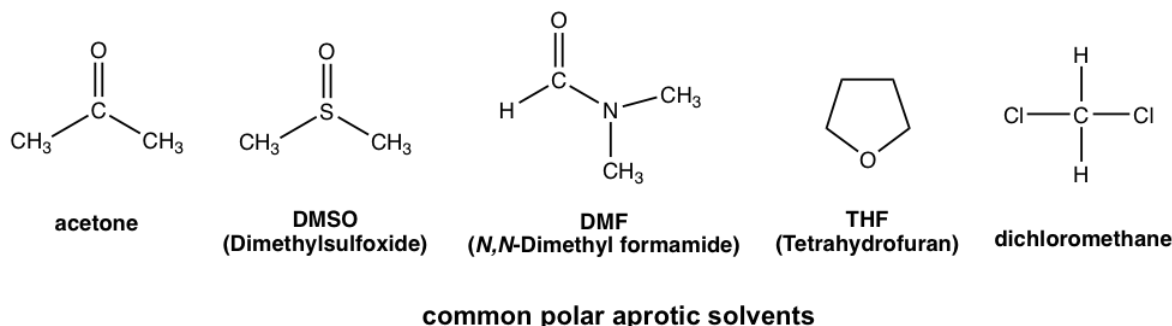
Solvents can be divided into **three** major categories based on the structures and polarities, that is: non-polar, polar protic and polar aprotic solvents.



Non-polar solvents are non-polar compounds. (hexane, benzene, toluene, etc.)

Polar protic solvents are the compounds containing OH or NH group that is able to form hydrogen bonds. Polar protic solvents are highly polar because of the OH or NH group.

Polar aprotic solvents is a group of solvents with a medium range of polarity. They are polar because of polar bonds like C=O or S=O, but the polarity is not as high as OH or NH group. Typical examples of polar aprotic solvents include acetone, DMSO, DMF, THF, CH₂Cl₂.



The general guideline for solvents regarding nucleophilic substitution reaction is:

- S_N1 reactions are favored by polar protic solvents (H₂O, ROH etc), and usually are solvolysis reactions.
- S_N2 reactions are favored by polar aprotic solvents (acetone, DMSO, DMF etc).

Polar Protic Solvents Favor S_N1 Reactions

In S_N1 reaction, the leaving group leaves and carbocation formed in the first step, that is also the rate-determining step. The polar solvent, such as water, MeOH, is able to form hydrogen bonding with the leaving group in the transition state of the first step, therefore lowering the energy of the transition state that leads to the carbocation, and speed up the rate-determining step. As a result, polar protic solvents facilitate S_N1 reactions. It is very common that the polar protic solvents serve as nucleophiles as well for S_N1 reactions, so usually S_N1 reactions are solvolysis reactions as we learned earlier.

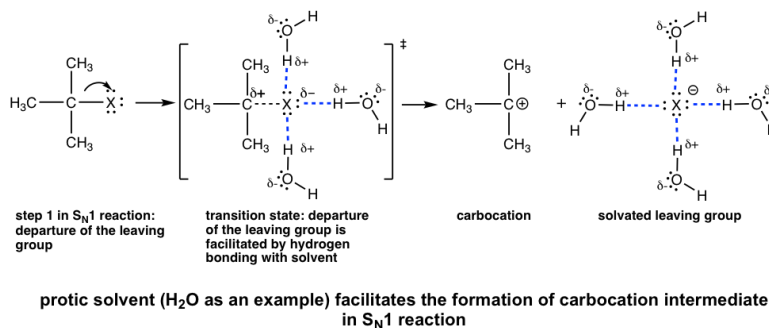
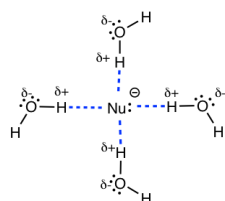


Figure 7.5a Protic solvent (ex. H₂O) facilitates the formation of carbocation intermediate in S_N1 reaction

Polar Aprotic Solvents Favor S_N2 Reactions

Strong nucleophiles are required in S_N2 reactions, and strong nucleophile are usually negatively charged species, such as OH⁻, CH₃O⁻, CN⁻ etc. These anions must stay with cations in salt format like NaOH, CH₃ONa etc. Since salts are insoluble in non-polar solvent, therefore non-polar solvents are not appropriate choices, and we need polar solvents that can dissolve the salts.

The issue for **polar protic** solvent is that the nucleophile anions will be surrounded by a layer of solvent molecules with hydrogen bonds, and this is called the solvation effect. The solvation effect stabilize (or encumber) the nucleophiles and hinder their reactivities in S_N2 reaction. Therefore, polar protic solvents are not suitable for S_N2 reactions.


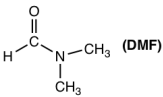


**protic solvent does not work for S_N2:
nucleophile is solvated and encumbered by protic solvent**

Figure 7.5b Protic solvent does not work for S_N2: nucleophile is solvated and encumbered by protic solvent

As a result the **polar aprotic** solvents, such as acetone, DMSO etc are the best choice of S_N2 reactions. They are polar enough to dissolve the salt format nucleophiles, and also not interact as strongly with anions to hinder their reactivities. The nucleophile anions still move around freely in polar aprotic solvent to act as nucleophile.

The reaction rate for a S_N2 reaction in different solvents are provided in the table below, and the polar aprotic solvent DMF proved to be the best choice that speed up the reaction significantly.

reaction: $\text{CH}_3\text{I} + \text{Cl}^- \rightarrow \text{CH}_3\text{Cl} + \text{I}^-$	
solvent	relative rate
CH_3OH	1
	12.5
 (DMF)	1,200,000

7.5.3 The Choice of Reaction Pathway: S_N1 or S_N2 ?

With all the knowledge about S_N1 , S_N2 reactions and reaction conditions, we should be able to determine that whether a given reaction go with S_N1 or S_N2 pathway, or design a proper reaction that will produce the desired product(s). The reaction pathway predominantly depends on the nature of the substrates (primary, secondary or tertiary), and the choice of proper reaction condition serve as a way to facilitate the process.

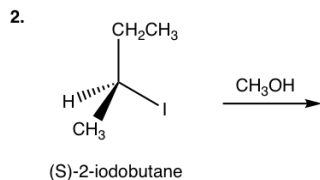
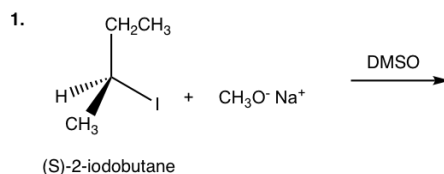
- Primary and methyl substrates undergo S_N2 reaction predominantly.
- Tertiary substrates go with S_N1 process.
- The reaction of secondary substrates mainly rely on the conditions applied. The condition include nucleophile, solvent, etc. See examples for more detailed discussions.

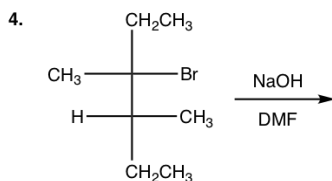
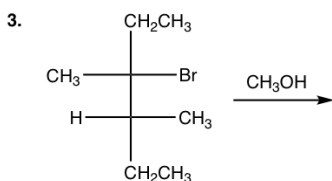
Exercises 7.4

Show the product(s) of the following reactions:

1. (S)-2-iodobutane + $\text{CH}_3\text{O}^- \text{Na}^+$ (DMSO \rightarrow _

2. (S)-2-iodobutane ($\text{CH}_3\text{OH} \rightarrow$ _



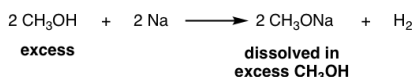


Answers to Practice Questions Chapter 7

Some practical tips for working on S_N1, S_N2 reactions:

- As we understand that strong nucleophiles are required for S_N2 reaction, and most of the strong nucleophiles are those with negative charges, for example OH⁻, OR⁻. These nucleophiles can be either shown as anions OH⁻, CH₃O⁻, C₂H₅O⁻, **or** in salt format like NaOH, KOH, CH₃ONa, C₂H₅ONa in the reaction conditions. You should understand that it is the same thing. The anion format are easy to identify and also highlight the nature of these species, however since anions must stay together with counter cations as salt, the salt format show the actual chemical formula of the compound used in the reaction.
- Since polar aprotic solvent favors S_N2 reactions, so any of above anions or salt can be used together with DMSO, DMF etc, such as OH⁻/DMSO, CH₃ONa/DMF etc .

However, sometimes you may see the combination like CH₃ONa/CH₃OH, that is the combination of CH₃O⁻ together with its conjugate acid CH₃OH. It may seems contradictory, why a strong nucleophile for S_N2 combine with solvent for S_N1? The reality is that CH₃ONa here still act as strong nucleophile and can be used for S_N2 reaction and CH₃OH is the solvent for CH₃ONa. The reason why CH₃OH is used together as solvent is that the CH₃ONa can be prepared by treating an alcohol with Na. For example:



Other alcohol can also react with Na metal (or potassium metal, K) to generate the corresponding R₄Na.

The reaction between alcohol and NaH can be used as well.



ROH + NaH \longrightarrow RNa + H₂ Since alcohol are in excess in the above reactions, it is also a good solvent for the resulting alkoxide, and RO⁻/ROH combination is used commonly together. The RO⁻ in this combination can be used as strong nucleophile for S_N2 reaction, or base in elimination reaction (**Chapter 8**).

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