

NUCLEOPHILICITY

WHAT IS A NUCLEOPHILE ? A BASE ?

WHAT MAKES A GOOD NUCLEOPHILE?

NUCLEOPHILES AND BASES

THE FUNDAMENTAL DISTINCTION

Nucleophilicity

kinetic (or rate) parameter

Basicity

thermodynamic (or equilibrium) parameter.

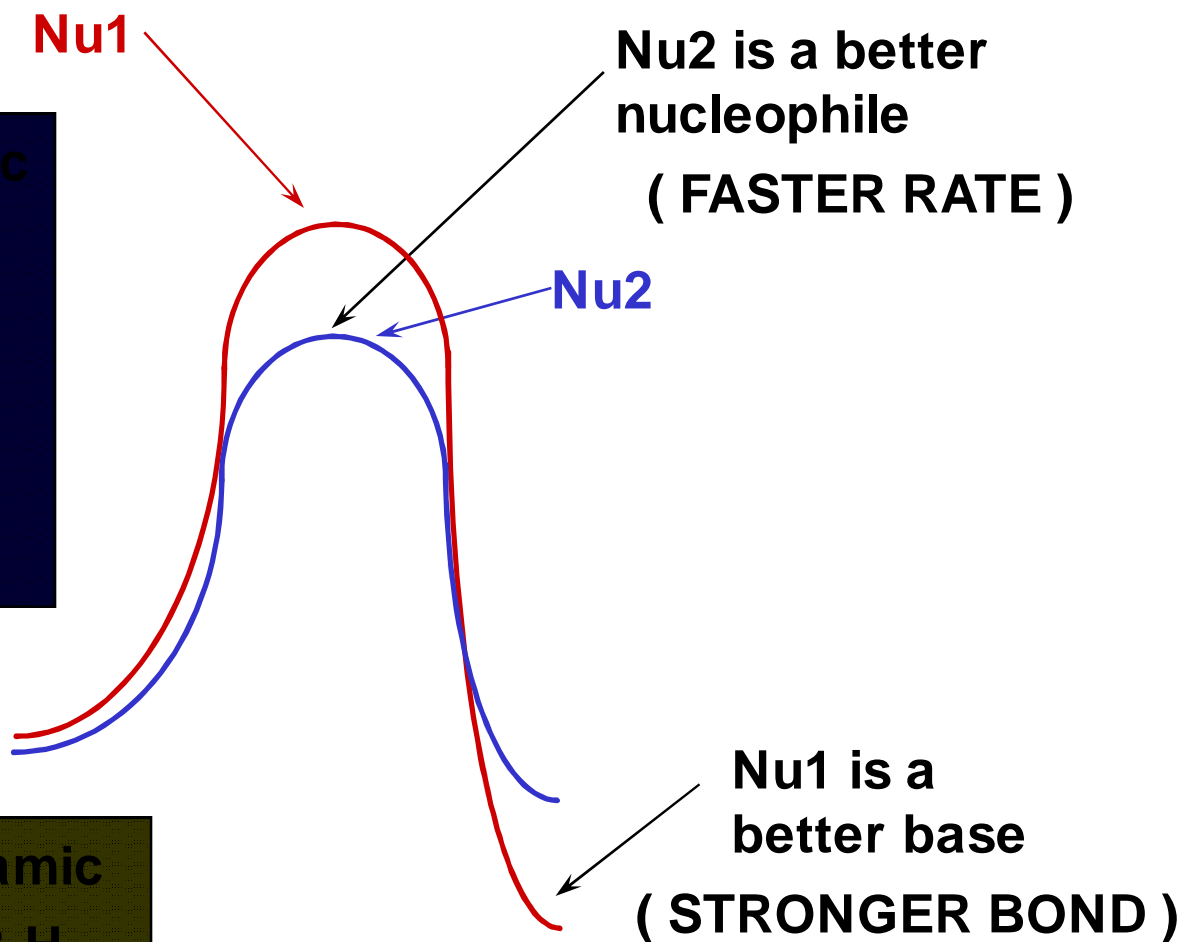
**All nucleophiles are bases
and all bases are nucleophiles.**

HOWEVER : **A good base is not necessarily
a good nucleophile, and vice versa.**

NUCLEOPHILE VERSUS BASE

Nucleophilicity = Kinetic
Rate = $k_2[RX][Nu]$
↑
good nucleophile
increases k_2
(I.e., the rate)

Basicity = Thermodynamic
 $B:^- + H^+ \rightleftharpoons B-H$
strong base
shifts equilib. →



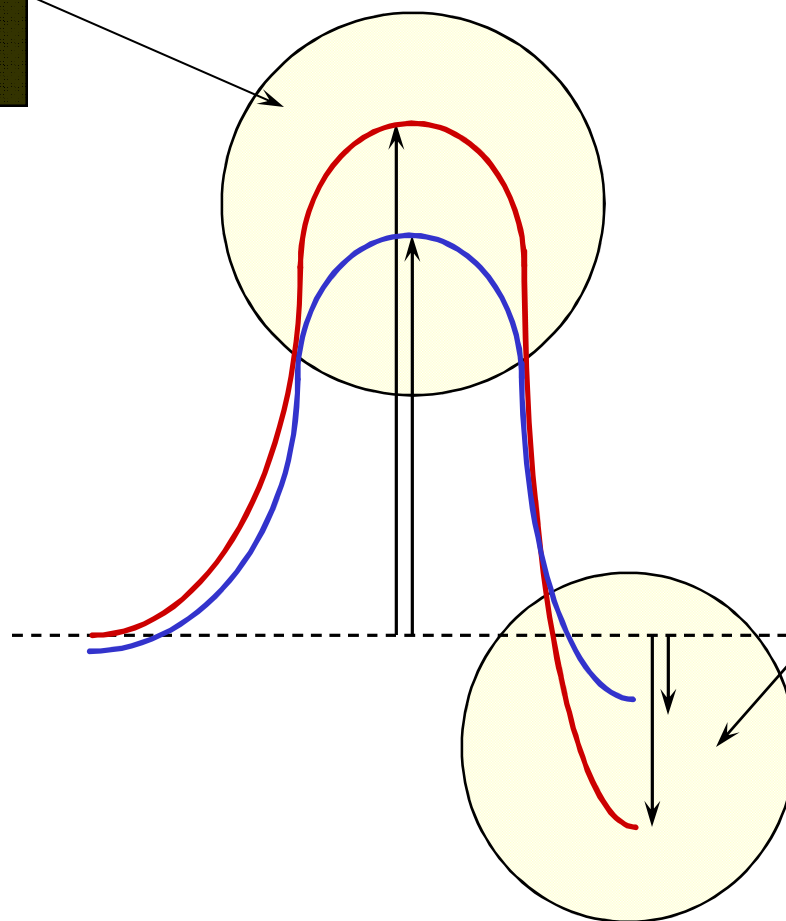
DIFFERENT PLACES ON THE ENERGY PROFILE DETERMINE NUCLEOPHILICITY AND BASICITY

NUCLEOPHILES

Nucleophilicity is determined here

activation energy and rate (kinetics)

faster is better



BASES

Basicity is determined here

strength of bonds and position of equilibrium

lower energy is better

**IS THE NUCLEOPHILE IMPORTANT
IN BOTH S_N1 AND S_N2 REACTIONS ?**

NUCLEOPHILES

IMPORTANCE IN S_N1 AND S_N2 REACTIONS

Nucleophiles are unimportant in an S_N1 reaction; they are not involved in the rate-determining step.

$$S_N1 \text{ rate} = k_1 [RX]$$

The nature of a nucleophile is only important to an S_N2 reaction.

$$S_N2 \text{ rate} = k_2 [RX][Nu]$$



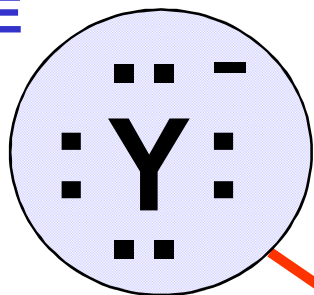
**WHAT IS A
GOOD NUCLEOPHILE ?**

S_N2 REACTIONS

WHAT IS THE IDEAL NUCLEOPHILE ?

S_N2 REACTIONS

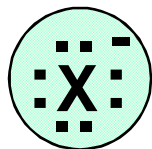
LARGE



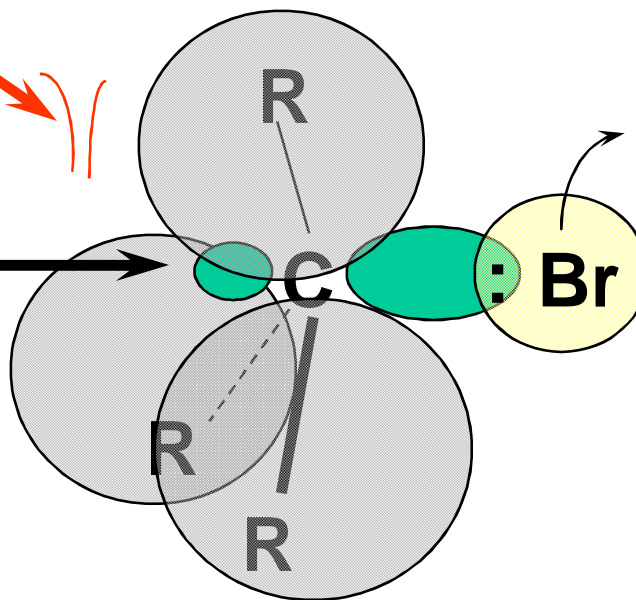
STERIC PROBLEMS

no way ! bad

SMALL



good



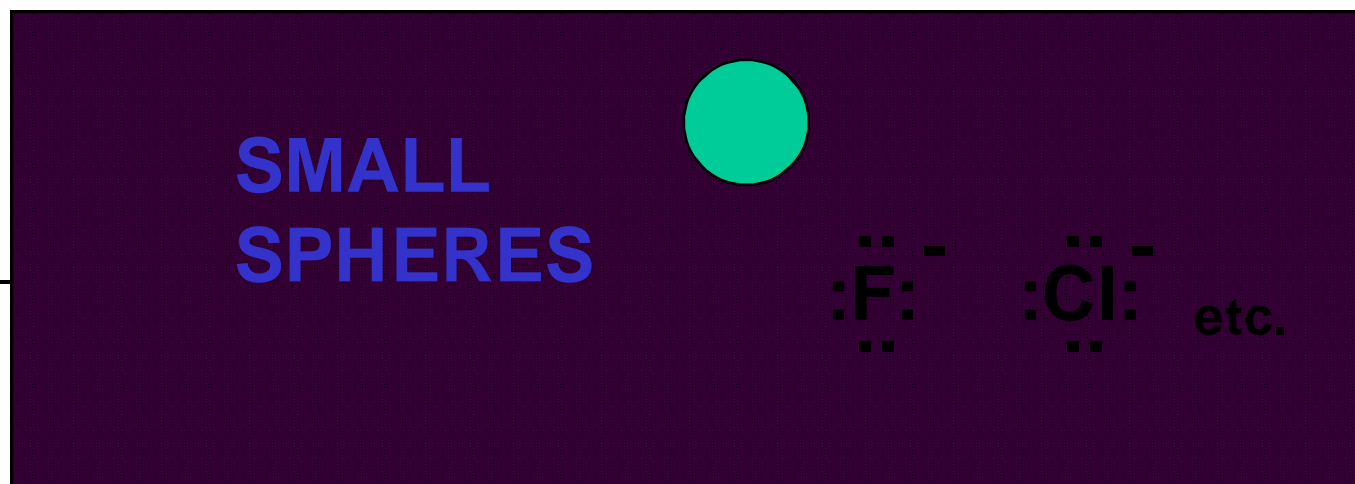
Smaller
is better !

For an S_N2 reaction the nucleophile must find the back lobe of the sp^3 hybrid orbital that the leaving group is bonded to.

EXPECTED "IDEAL" NUCLEOPHILES



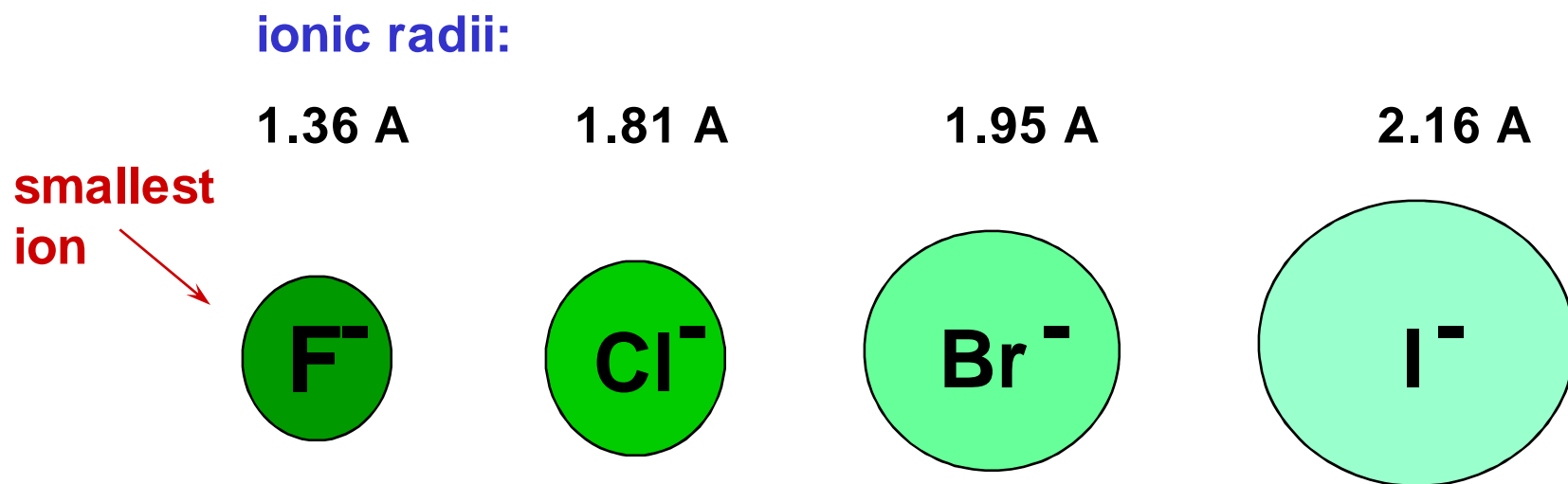
These types should be able to find the target !



Generally this idea is correct.

OUR NAÏVE EXPECTATION

We would expect the halides to be good nucleophiles:



and we would expect the smallest one (fluoride) to be the best nucleophile,

..... however, that is not usually the case.

EXPERIMENTAL RESULTS

RELATIVE RATES OF REACTION FOR THE HALIDES



$$\text{Rate} = k [\text{CH}_3\text{I}] [\text{X}^-]$$

S_N2

	k	
F ⁻	5 x 10 ²	slowest
Cl ⁻	2.3 x 10 ⁴	
Br ⁻	6 x 10 ⁵	
I ⁻	2 x 10 ⁷	fastest

* MeOH solvates like water but dissolves everything better.

SOLVATION

Solvation reverses our ideas of size.

HEAT OF SOLVATION

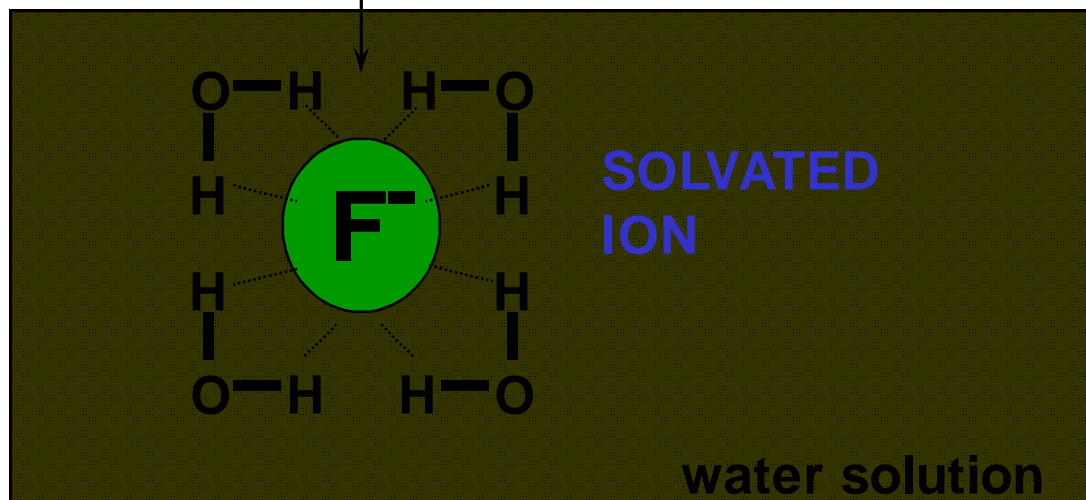
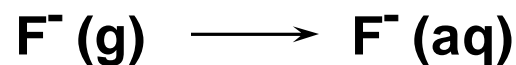
ENERGY IS RELEASED WHEN AN ION IS PLACED IN WATER



gas phase

- 120 Kcal / mole

HEAT OF SOLVATION



The interaction between the ion and the solvent is a type of weak bond. Energy is released when it occurs.

Solvation lowers the potential energy of the nucleophile making it less reactive.

HALIDE IONS

IONIC
RADIUS

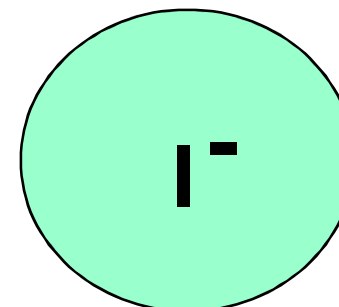
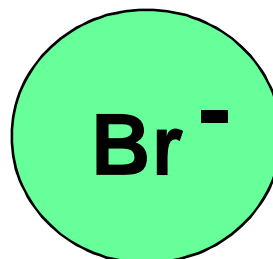
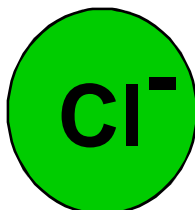
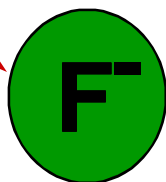
1.36 Å

1.81 Å

1.95 Å

2.16 Å

smallest
ion



Heats of
solvation
in H_2O

- 120

- 90

- 75

- 65

Kcal / mole



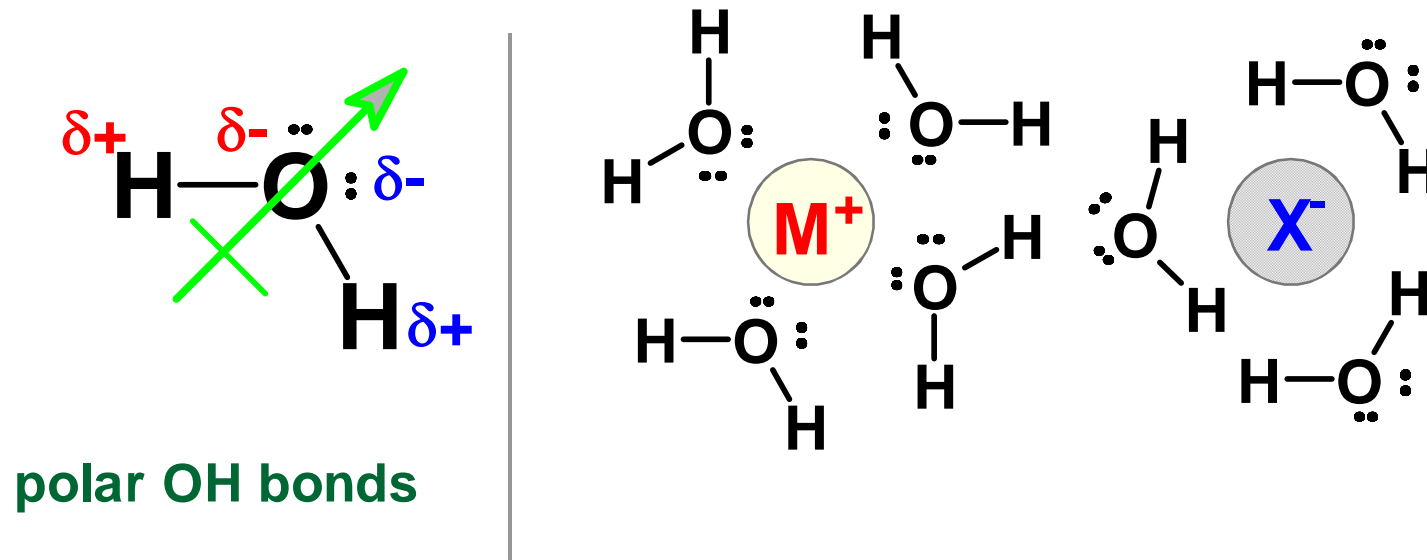
larger n

increasing solvation

smaller n

SMALL IONS SOLVATE MORE THAN LARGE IONS

WATER AS A SOLVENT

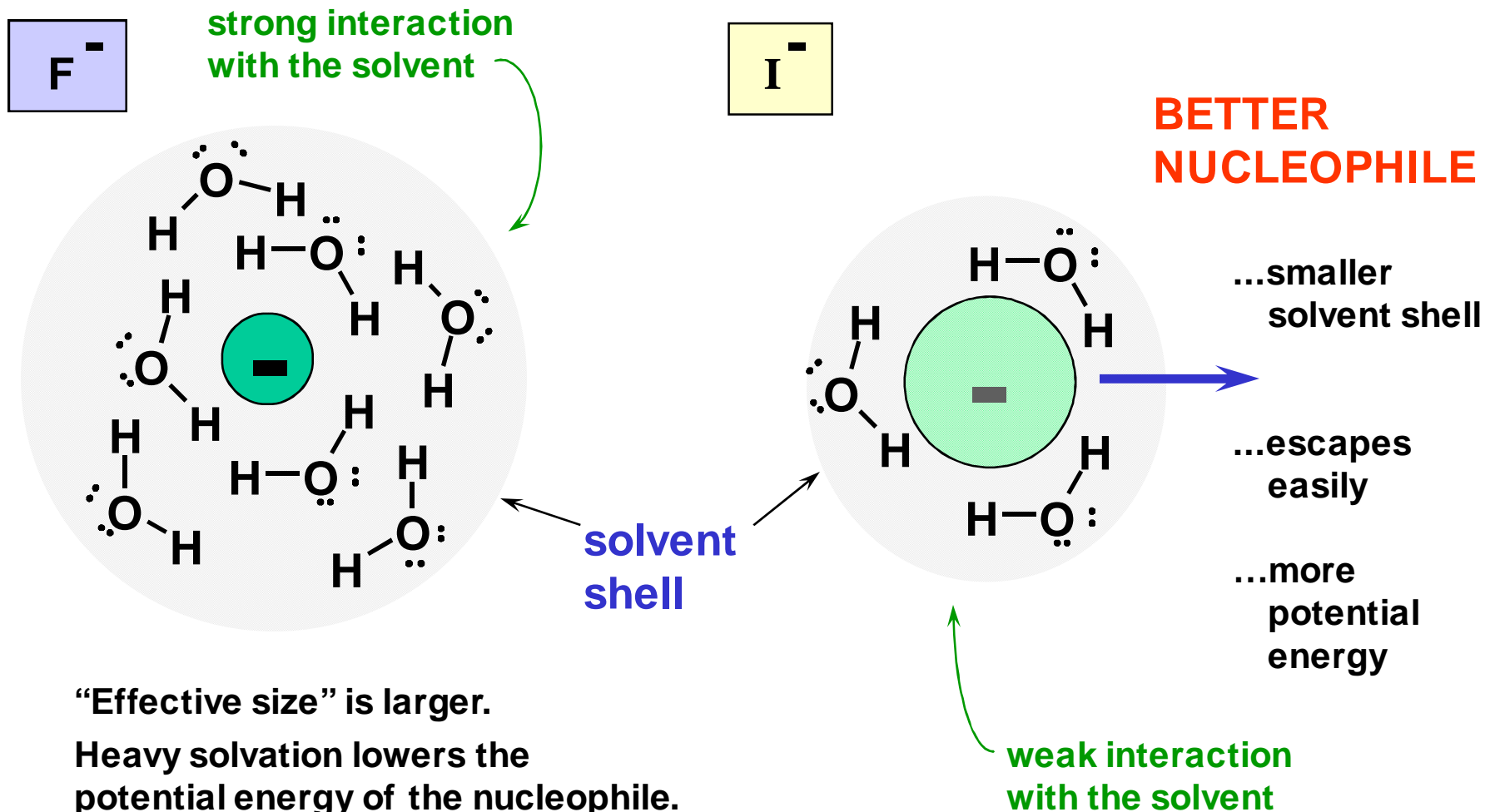


Water is a polar molecule.

Negative on the oxygen end, and positive on the hydrogen end.

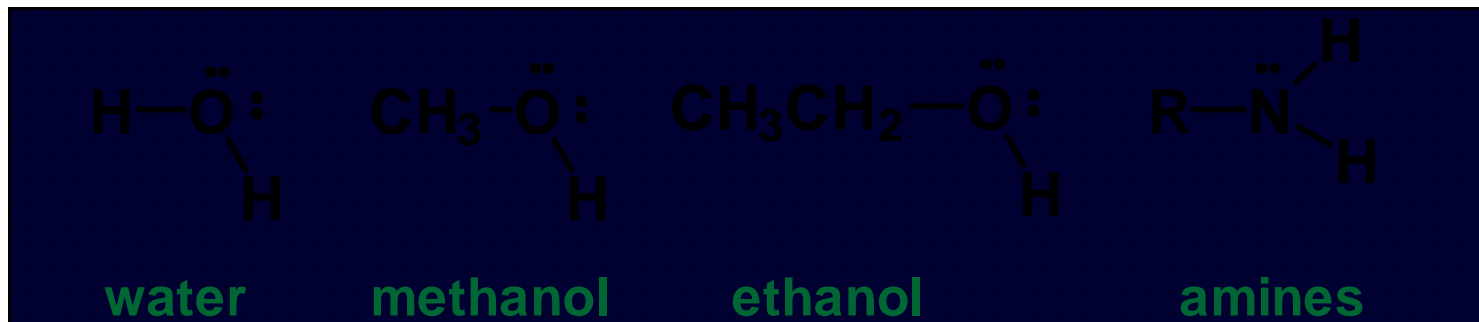
It can solvate both cations and anions.

SMALL IONS SOLVATE MORE HEAVILY THAN LARGE ONES



“Effective size” is larger.
Heavy solvation lowers the potential energy of the nucleophile.
It is difficult for the solvated nucleophile to escape the solvent shell.
This ion is less reactive.

PROTIC SOLVENTS



Water is an example of a “protic” solvent.

Protic solvents are those that have

O-H, N-H or **S-H** bonds.

Protic solvents can form hydrogen bonds and can solvate both cations and anions.

LARGER IONS ARE BETTER NUCLEOPHILES IN PROTIC SOLVENTS

THREE FACTORS ARE INVOLVED :

1

In protic solvents the larger ions are solvated less (smaller solvent shell) and they are, therefore, effectively smaller in size and have more potential energy.

2

Since the solvent shell is smaller in a larger ion it can more easily “escape” from the surrounding solvent molecules during reaction. There is more potential energy.

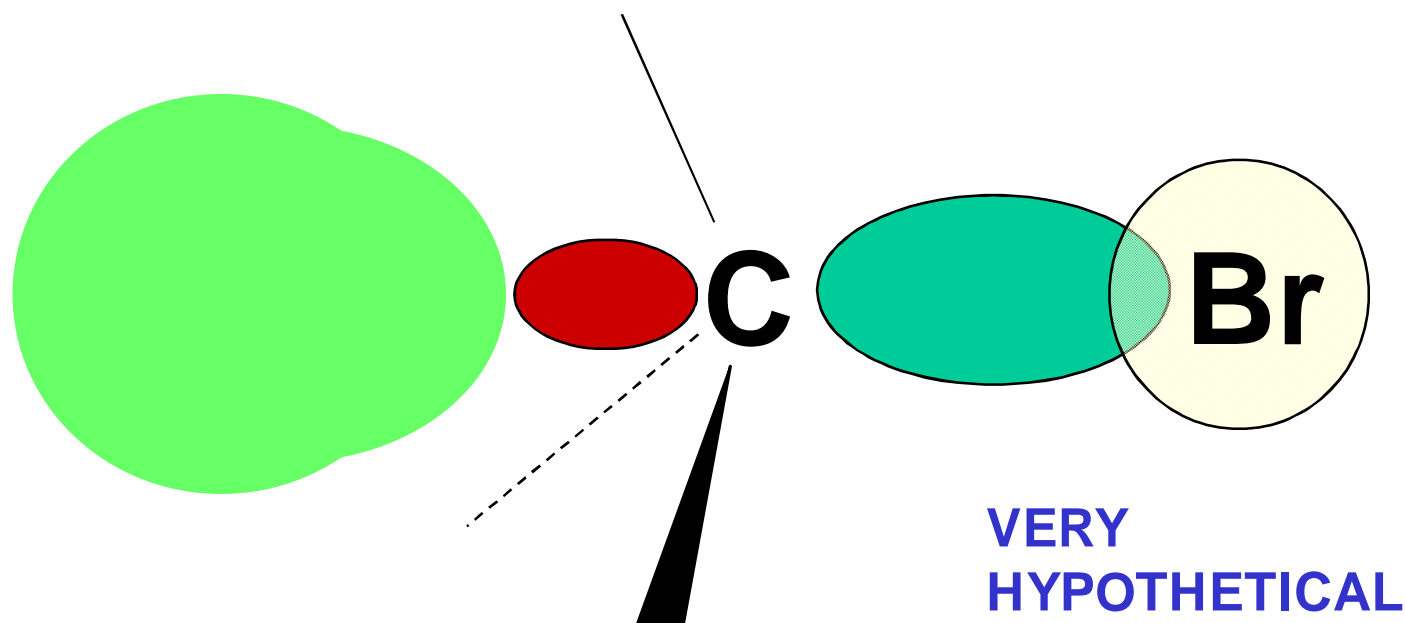
3

The larger ions are thought (**by some**) to be more “polarizable”.

see the next slide

POLARIZABILITY

Polarizability assumes larger ions are able to easily distort the electrons in their valence shell, and that smaller ions cannot.



The distortion of large ions is easier because the orbital clouds are more diffuse.

The nucleophile “flows” into the reactive site.

BASICITY

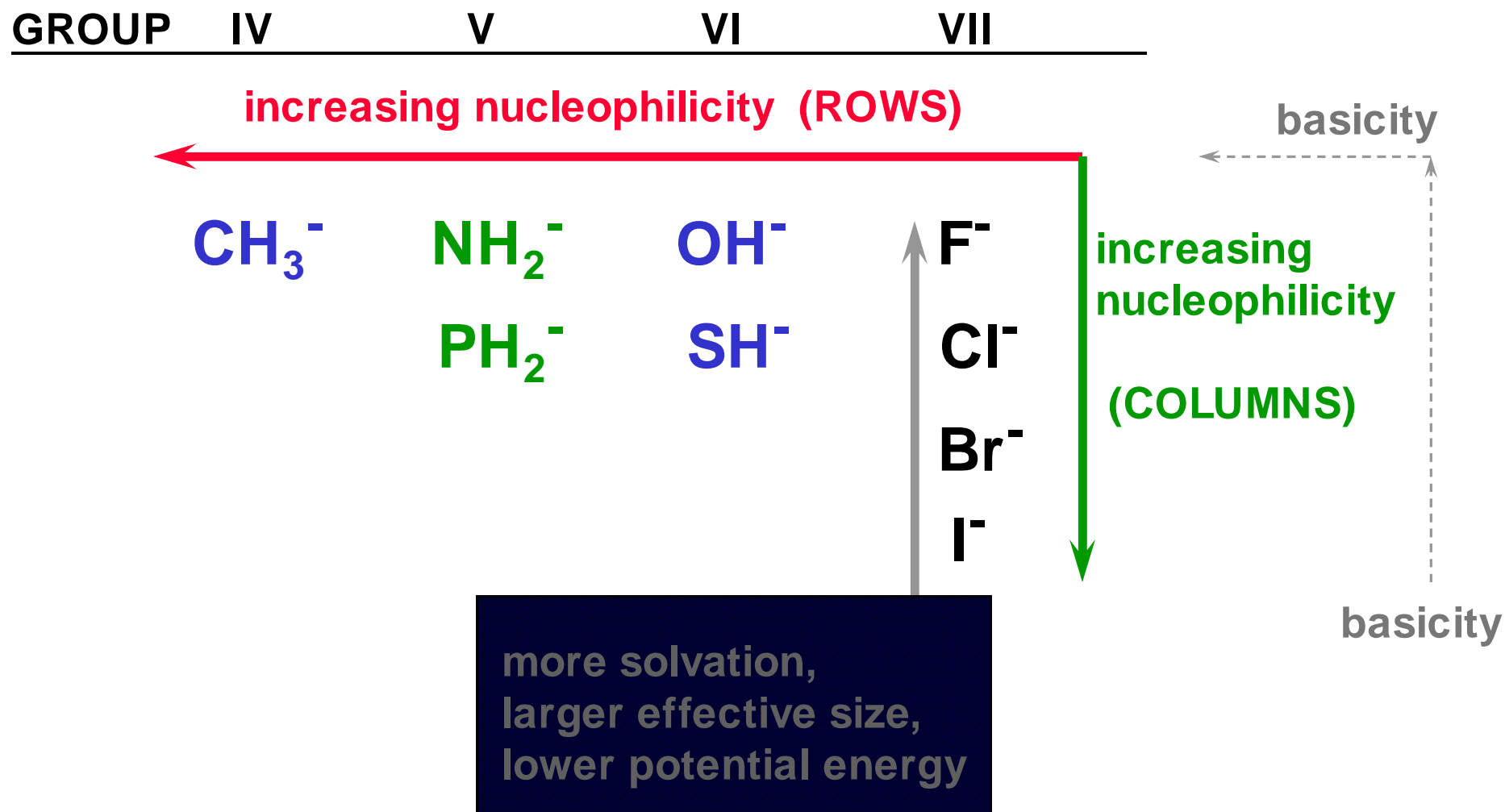
If everything else is equal, the stronger base is the better nucleophile.

This principle shows up in a period, where atoms do not vary appreciably in size, and solvate to similar extents.

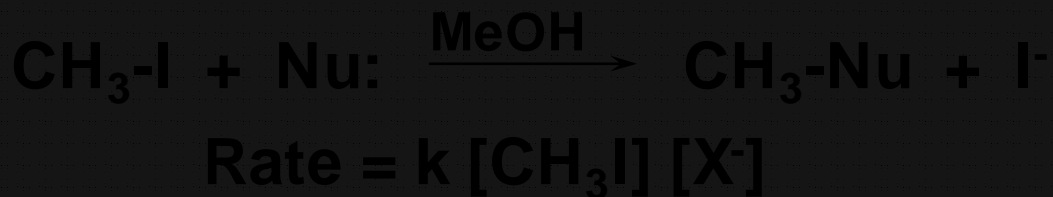
OH^- is a better nucleophile than F^-

NUCLEOPHILICITY TRENDS IN PROTIC SOLVENTS

OBSERVED NUCLEOPHILICITY TRENDS H₂O OR OTHER “PROTIC” SOLVENTS



RELATIVE RATES OF SOME NUCLEOPHILES



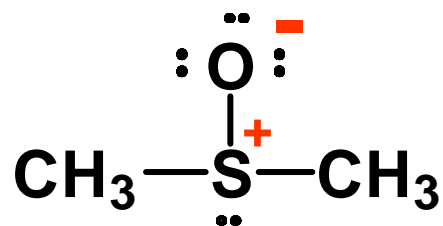
S_N2

		← CH ₃ OH	1.0 (solvolysis is faster)
F ⁻	5 x 10 ²		
CH ₃ COO ⁻	2 x 10 ⁴	← [NH ₃ (CH ₃) ₂ S C ₆ H ₅ NH ₂ C ₆ H ₅ SH]	3.2 x 10 ⁵ 3.5 x 10 ⁵ 5 x 10 ⁵ 5 x 10 ⁵
Cl ⁻	2.3 x 10 ²		
C ₆ H ₅ O ⁻	5.6 x 10 ⁵		
N ₃ ⁻	6 x 10 ⁵		
Br ⁻	6 x 10 ⁵		
CH ₃ O ⁻	2 x 10 ⁶		
CN ⁻	5 x 10 ⁶		
I ⁻	2 x 10 ⁷		
C ₆ H ₅ S ⁻	8 x 10 ⁹		
		← CHARGED →	← NEUTRAL →

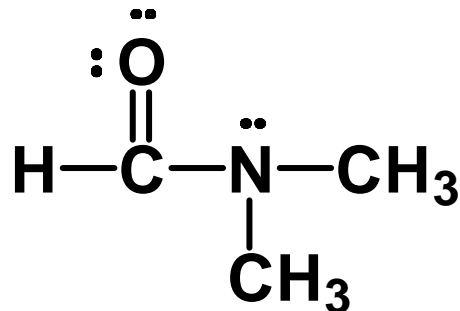
these are the good nucleophiles, but watch out, some are strong bases

APROTIC SOLVENTS

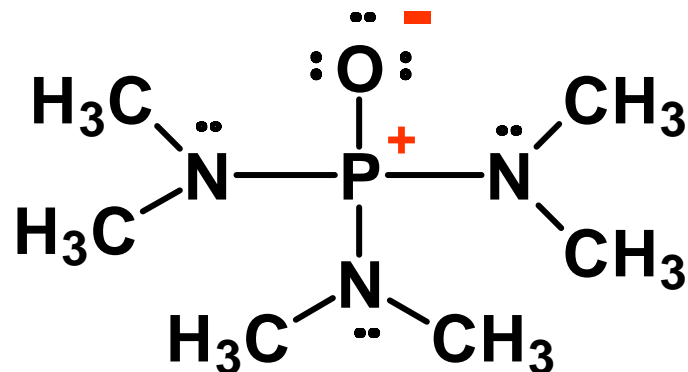
APROTIC SOLVENTS



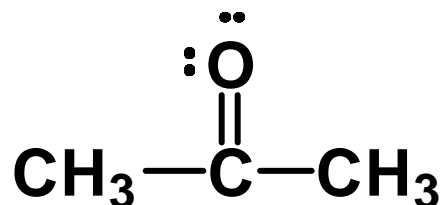
dimethylsulfoxide
"DMSO"



dimethylformamide
"DMF"



hexamethylphosphoramide
"HMPA"



acetone



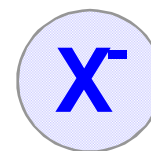
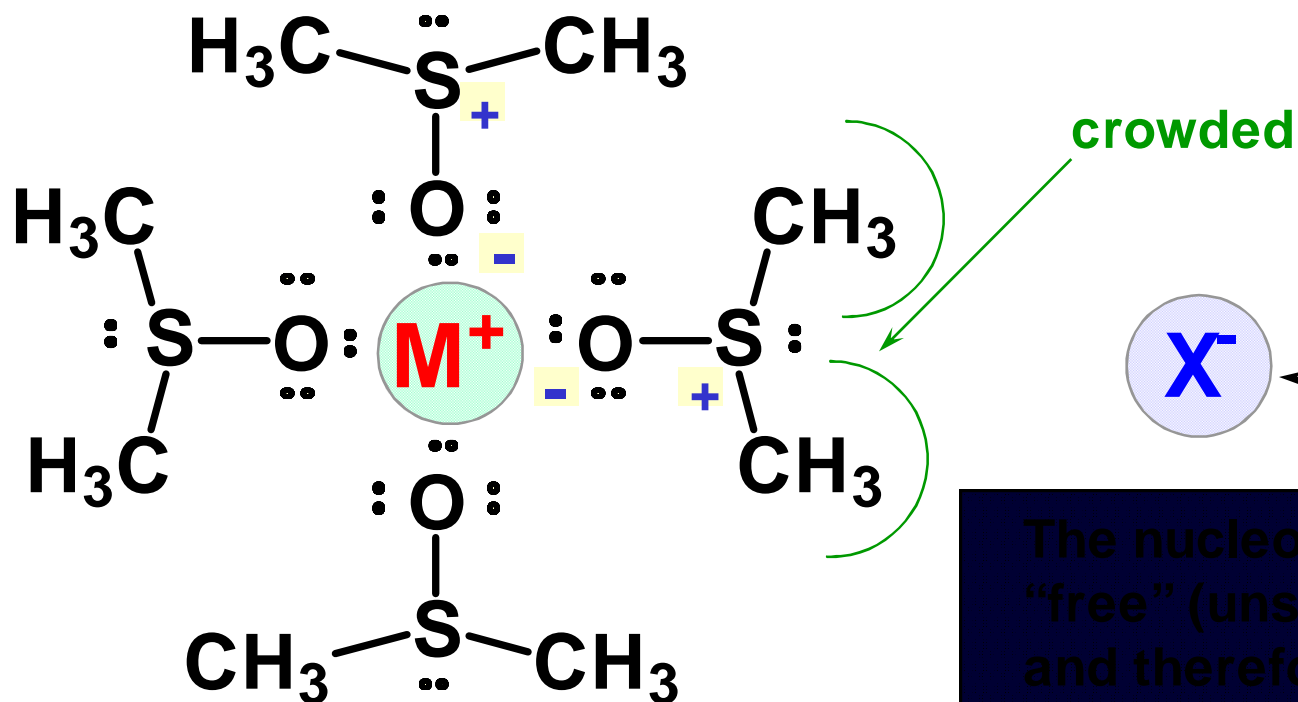
acetonitrile

if scrupulously
free of water

APROTIC SOLVENTS
DO NOT HAVE
OH, NH, OR SH BONDS

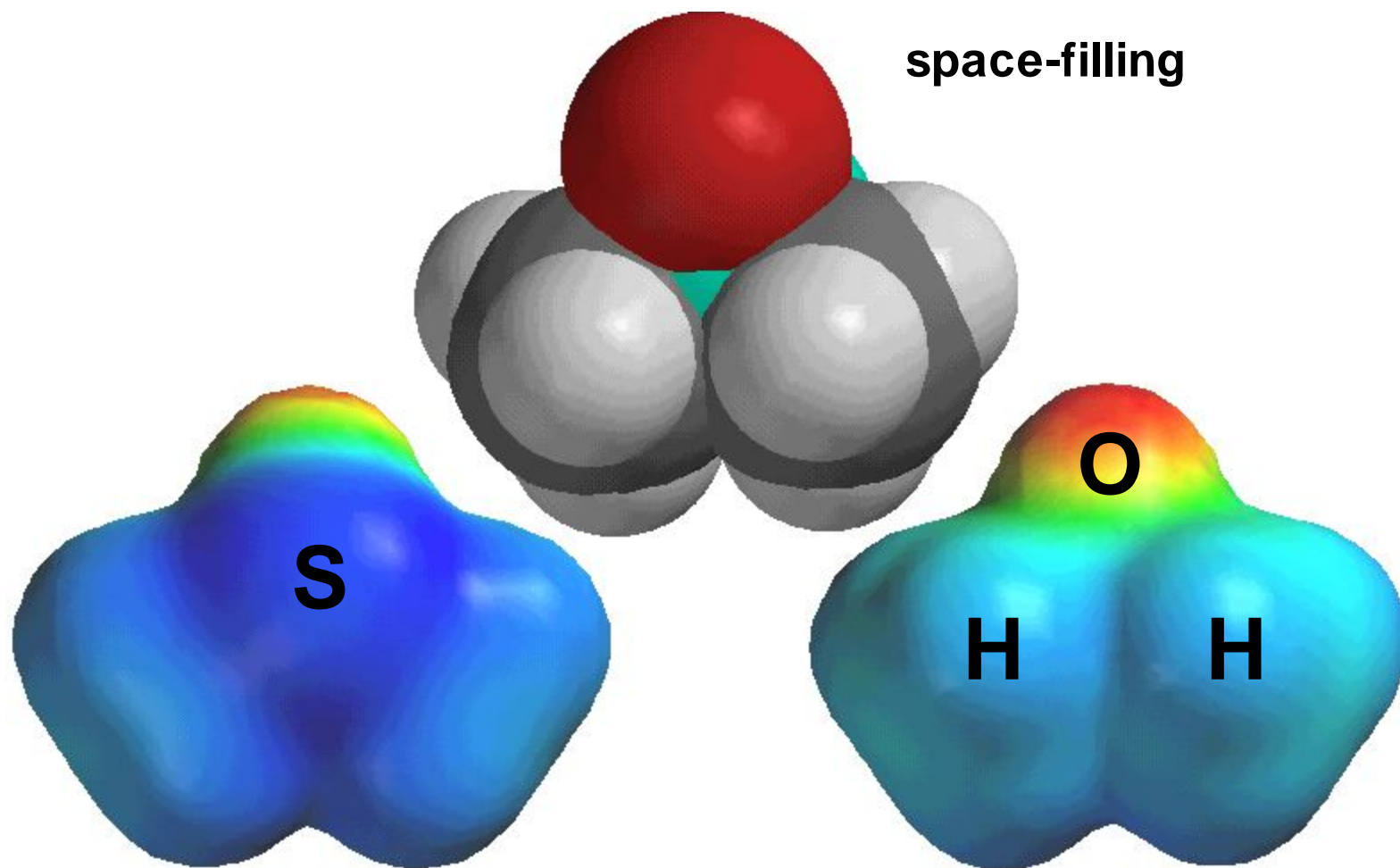
They do not form
hydrogen bonds.

APROTIC SOLVENTS SOLVATE CATIONS, BUT NOT ANIONS (NUCLEOPHILES)



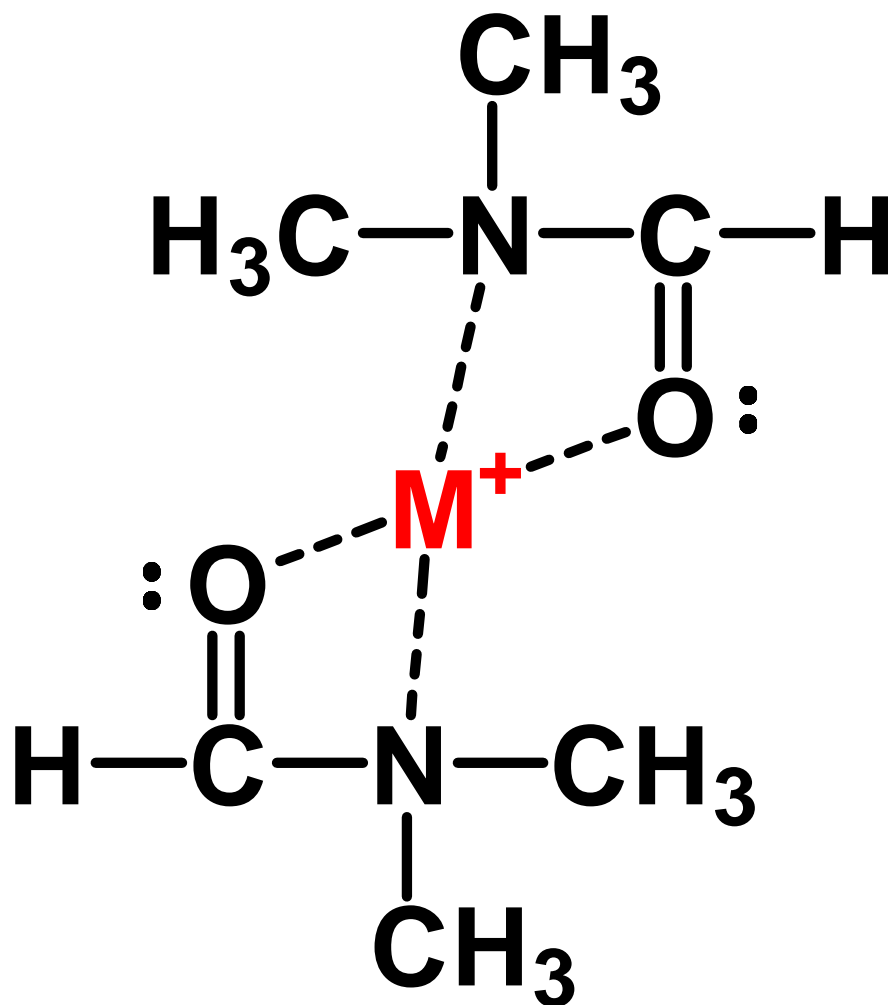
The nucleophile is "free" (unsolvated), and therefore is small and not hindered by a solvent shell.

DIMETHYLSUFOXIDE



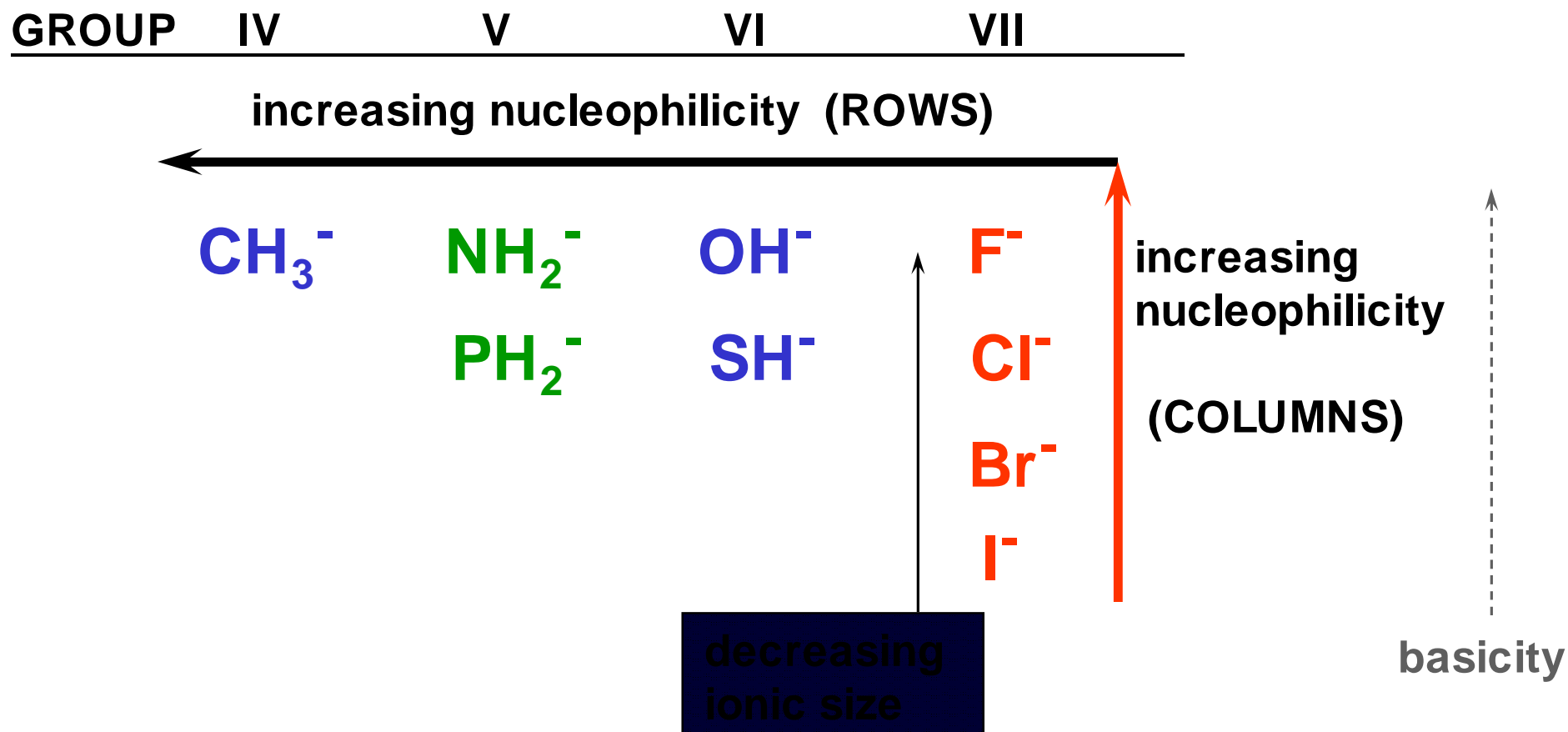
density - electrostatic potential plot

DIMETHYLFORMAMIDE



nucleophile is "free"
(unsolvated)

OBSERVED NUCLEOPHILICITY APROTIC SOLVENTS



The direction of the red arrow (COLUMNS) represents a different order than in protic solvents.

WHY NOT ALWAYS USE APROTIC SOLVENTS FOR S_N2 ?

Mostly, it is a matter of expense.

Water, ethanol, methanol and acetone are much cheaper, especially water.

Water	“free”	DMSO	\$47.50 / L
Methanol	\$14.70 / L	DMF	\$33.75 / L
Ethanol	\$15.35 / L	HMPA	\$163.40 / L
Acetone	\$16.60 / L		

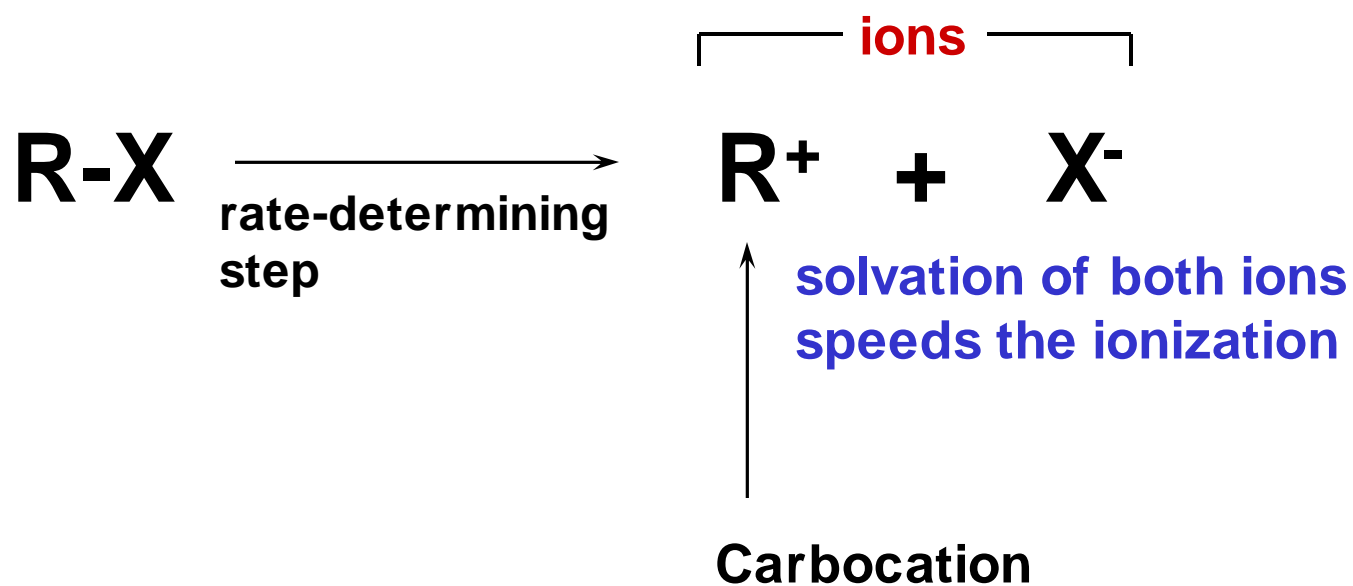
Cheapest grades available, Aldrich Chemical Co., 2000.

SOLVENTS

WHAT ARE GOOD SOLVENTS FOR S_N1 AND S_N2 ?

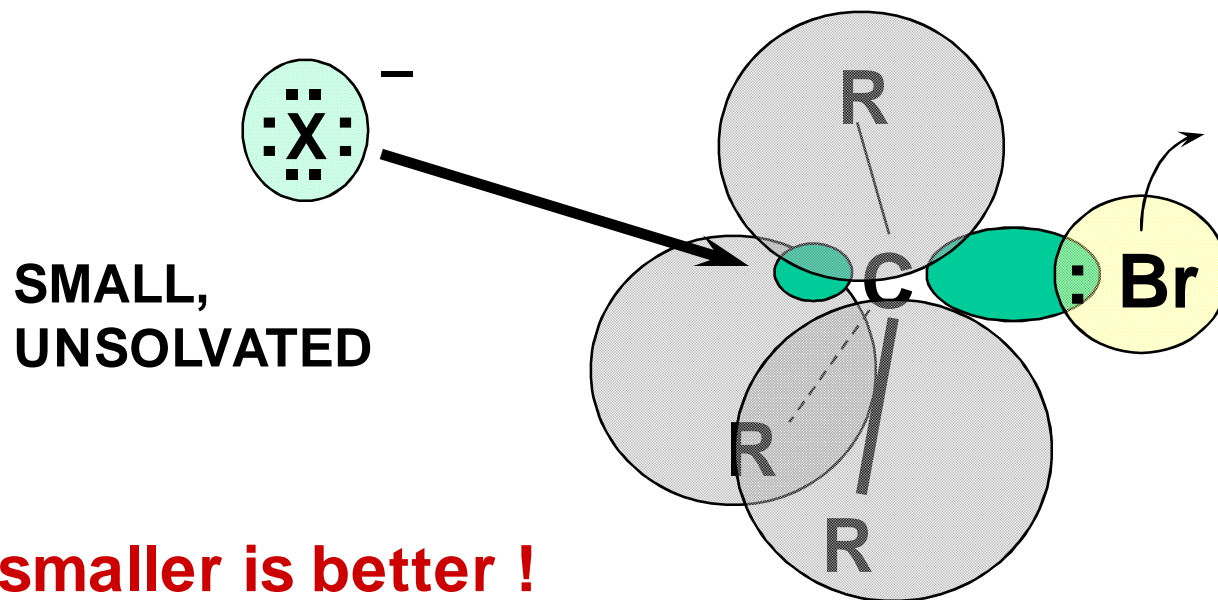
S_N1 SOLVENTS = POLAR

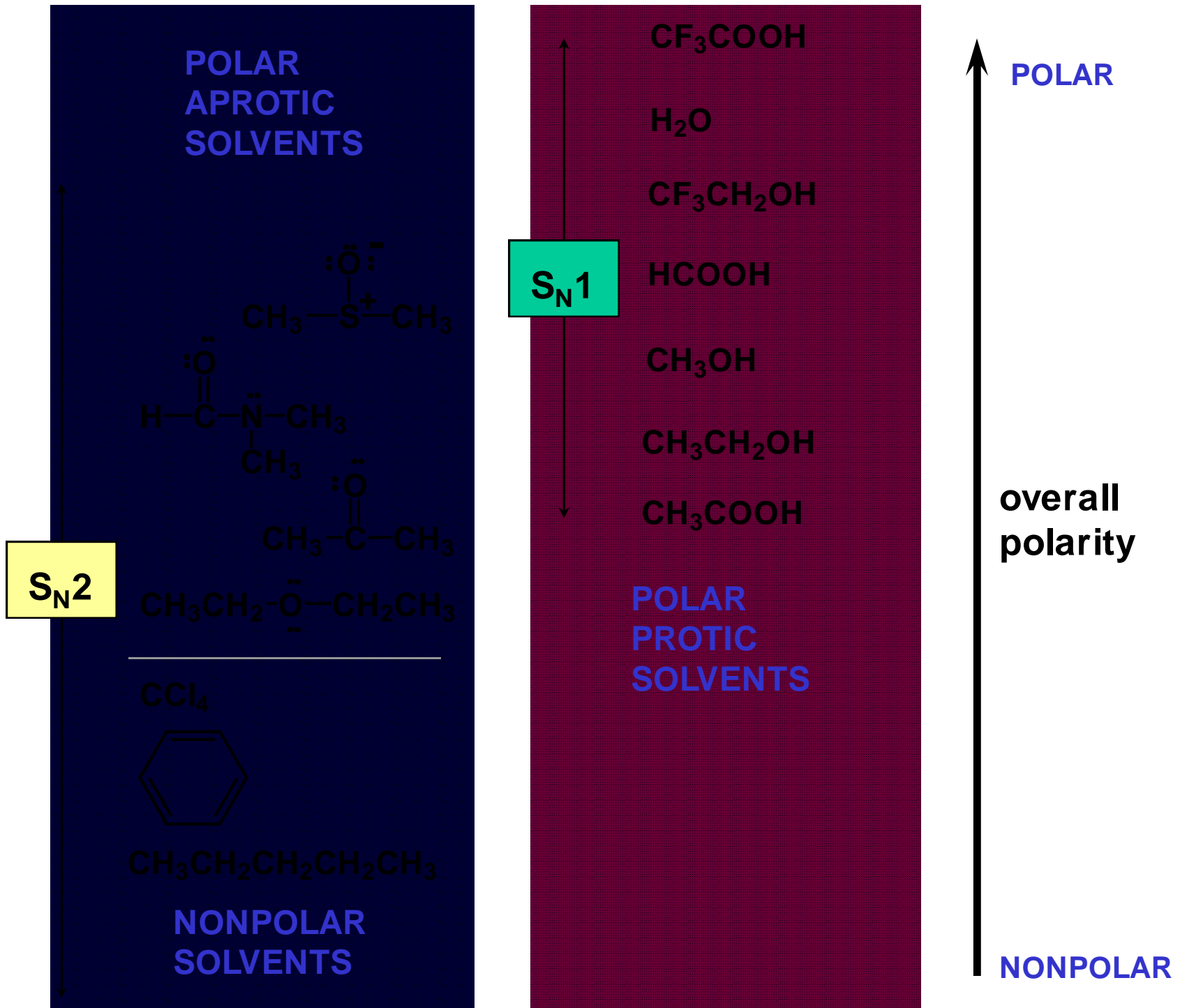
S_N1 reactions prefer polar-protic solvents that can solvate the anion and cation formed in the rate-determining step.



S_N2 SOLVENTS = NONPOLAR OR POLAR-APROTIC

S_N2 reactions prefer “non-polar” solvents, or polar-aprotic solvents that do not solvate the nucleophile.





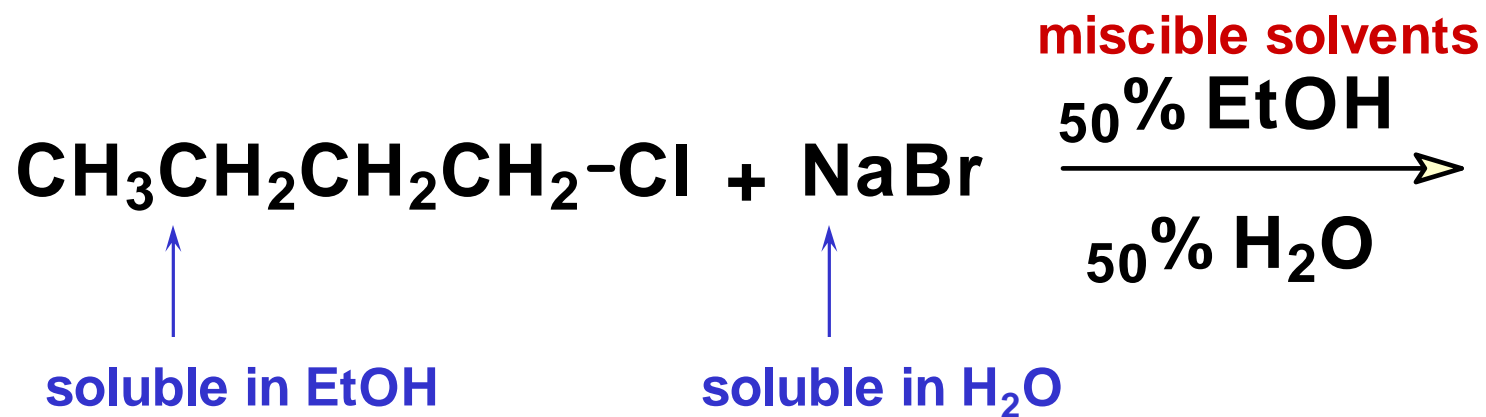
SOLVENT MIXTURES

SOLVENT MIXTURES ARE VERY COMMON

RX Alkyl halides don't dissolve in water, but dissolve in most organic solvents.

NaX Nucleophile salts don't dissolve in most organic solvents, but dissolve in water.

Both dissolve in a mixed solvent.



EXCEPTIONS

NaX

Dissolve in polar-aprotic organic solvents:
DMF, DMSO, HMPA.

NaI and NaCN dissolve in acetone,
but NaCl and NaBr do not

THE BOTTOM LINE

S_N1

CARBOCATIONS REACT WITH ALL NUCLEOPHILES EQUALLY

The nucleophile is not involved in the rate-determining step.

S_N2

BETTER NUCLEOPHILES REACT FASTER GIVING MORE PRODUCT

The nucleophile is involved in the rate-determining step.