

Q: How can you tell if a nucleophile is a good nucleophile or a bad nucleophile?

S_N2 reactions require a good nucleophile. Many students have asked me how we know if a nucleophile is a good nucleophile. Nucleophilicity (nucleophile strength) is a kinetic phenomenon, measured by comparing rates of reaction. Good nucleophiles have fast rates of S_N2 reactions.

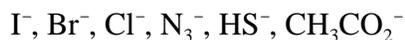
The following page shows the relative rates of reaction of various different nucleophiles with methyl iodide in methanol as a solvent. These are relative rates, so the rates were all compared to reaction of methyl iodide with methanol. So that is why methanol has a relative rate of 1 in the chart. Notice the relative rate of water is also 1. So methanol and water have the same nucleophile strength, and they are both bad nucleophiles relative to everything else on the chart. Remember this.

Don't memorize this chart – just notice a few trends.

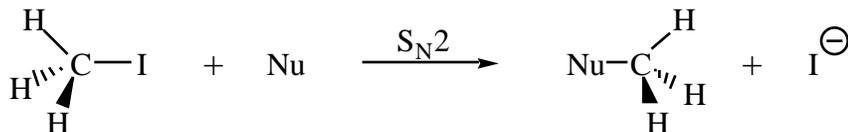
1. **Increasing negative charge increases nucleophilicity.** Water and methanol are bad nucleophiles, but if you deprotonate them, they become good nucleophiles.
2. **Nucleophilicity decreases to the right in the periodic table.** So nitrogen is more nucleophilic than oxygen which is more nucleophilic than fluorine. Notice you don't even need to deprotonate nitrogen for it to be a good nucleophile (look at NH_3 compared to H_2O .)
3. **Since this reaction was run in a polar protic solvent, Nucleophile strength increases as you go down a row in the periodic table.** So HS^- is more nucleophilic than HO^- , and I^- is more nucleophilic than Cl^- in methanol. If you were in a polar aprotic solvent, Cl^- would be more nucleophilic than I^- . But that's not so critical to remember. The truth of the matter is that *all of these nucleophiles will have faster S_N2 reactions in polar aprotic solvents*. So why aren't all S_N2 reactions run in polar aprotic solvents if they are all going to be faster? It is because many of the polar aprotic solvents are inconvenient to use. Both DMF and DMSO are high boiling. The solvent can't be easily removed on a rotary evaporator and if you put a reaction mixture run in DMF or DMSO in a separatory funnel in order to do an aqueous work-up, these two solvents will not form a separate layer from water. If you add ether, The DMF and DMSO will make the ether and water layers mix. So they often a big hassle to work with.

The basicity of a nucleophile is important when you want to favor S_N2 on a hindered alkyl halide, like a secondary alkyl halide. Some good nucleophiles are strong bases, and some are weak bases. Base strength is measured by looking at the pK_a of the conjugate acid. A weak base will have a conjugate acid with a pK_a less than about 8.

Here are some good nucleophiles from the following page that are weak bases:



Relative Rates of S_N2 Reaction of Various Nucleophiles with Iodomethane in Methanol:



Nucleophile	Relative Rate
H ₂ O	1
CH ₃ OH	1
F [⊖]	500
CH ₃ CO [⊖]	20,000
Cl [⊖]	23,500
NH ₃	316,000
PhO [⊖]	630,000
N ₃ [⊖]	630,000
Br [⊖]	630,000
CH ₃ O [⊖]	1,995,000
HO [⊖]	3,163,000
(CH ₃ CH ₂) ₃ N	5,010,000
CN [⊖]	5,010,000
I [⊖]	25,100,000
(CH ₃ CH ₂) ₃ P	501,000,000
HS [⊖]	1,000,000,000
PhS [⊖]	7,943,000,000
PhSe [⊖]	50,000,000,000