Nucleophilicity

Recall the definitions of electrophile and nucleophile:

**Electrophile**: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.

**Nucleophile**: An atom, ion or molecule that has an electron pair that may be donated in forming a covalent bond to an electrophile (or Lewis acid).

If we use a common alkyl halide, such as methyl bromide, and a common solvent, ethanol, we can examine the rate at which various nucleophiles substitute the methyl carbon. **Nucleophilicity** is thereby related to the relative rate of substitution reactions at the halogen-bearing carbon atom of the reference alkyl halide. The most reactive nucleophiles are said to be more nucleophilic than less reactive members of the group. The nucleophilicities of some common \( \text{Nu}^{(-)} \) reactants vary as shown in the following:

**Nucleophilicity**: \( \text{CH}_3\text{CO}_2^{(-)} < \text{Cl}^{(-)} < \text{Br}^{(-)} < \text{N}_3^{(-)} < \text{CH}_3\text{O}^{(-)} < \text{CN}^{(-)} \approx \text{SCN}^{(-)} < \text{I}^{(-)} < \text{CH}_3\text{S}^{(-)} \)

The reactivity range encompassed by these reagents is over 5,000 fold, thiolate being the most reactive. Note that by using methyl bromide as the reference substrate, the complication of competing elimination reactions is avoided. The nucleophiles used in this study were all anions, but this is not a necessary requirement for these substitution reactions. Indeed reactions 6 & 7, presented at the beginning of this section, are examples of neutral nucleophiles participating in substitution reactions. The cumulative results of studies of this kind has led to useful empirical rules pertaining to nucleophilicity:

1. **(i)** For a given element, negatively charged species are more nucleophilic (and basic) than are equivalent neutral species.
2. **(ii)** For a given period of the periodic table, nucleophilicity (and basicity) decreases on moving from left to right.
3. **(iii)** For a given group of the periodic table, nucleophilicity increases from top to bottom (i.e. with increasing size), although there is a solvent dependence due to hydrogen bonding. Basicity varies in the opposite manner.

Solvent Effects

**Solvation** of nucleophilic anions markedly influences their reactivity. The nucleophilicities cited above were obtained from reactions in methanol solution. Polar, protic solvents such as water and alcohols solvate anions by hydrogen bonding interactions, as shown in the diagram below.

These solvated species are more stable and less reactive than the unsolvated "naked" anions. Polar, aprotic solvents such as DMSO (dimethyl sulfoxide), DMF (dimethylformamide) and acetonitrile do not solvate anions nearly as well as methanol, but provide good solvation of the accompanying cations. Consequently, most of the nucleophiles discussed here react more rapidly in solutions prepared from these solvents. These solvent effects are more pronounced for small basic anions than for large weakly basic anions. Thus, for reaction in DMSO solution we observe the following reactivity order:
**Nucleophilicity:** $I^(-) < SCN^(-) < Br^(-) < Cl^(-) \approx N_3^(-) < CH_3CO_2^(-) < CN^(-) = CH_3S^(-) < CH_3O^(-)$

Note that this order is roughly the order of increasing basicity.

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