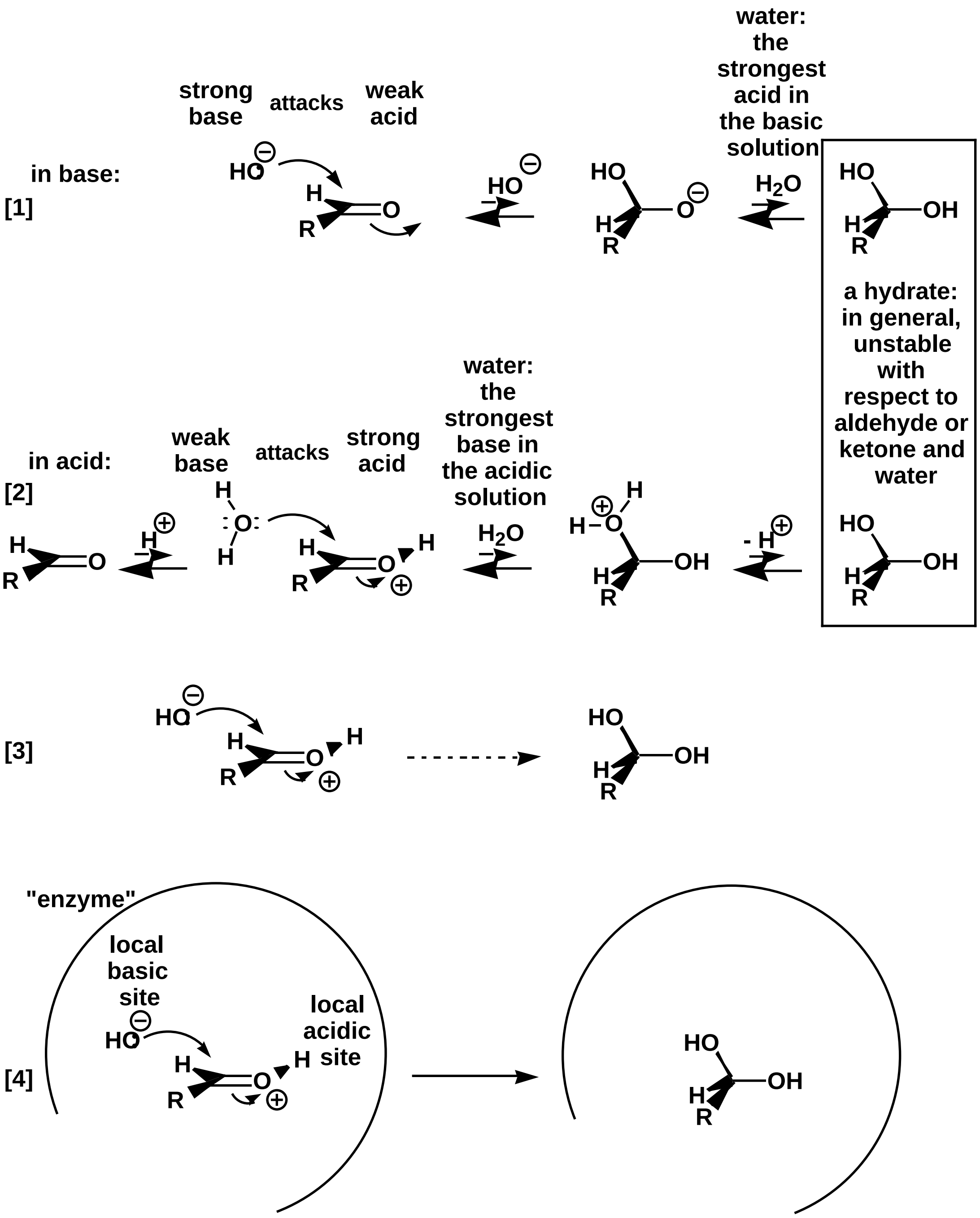
Text Related to Segment 18.01 ©2002 Claude E. Wintner

What about that most familiar of nucleophiles, hydroxide anion? It, too, behaves according to the carbonyl addition paradigm:



hydrate formation from aldehydes or ketones:
in base, in acid, and by a formalized "enzyme"

As in the figure, hydroxide anion attacks the carbonyl group of an aldehyde or ketone to form an intermediate oxyanion which then can gain a proton from the strongest acid in the basic solution, that is, water [1]. The product thus obtained, the result of addition of water to the carbonyl group, and called a hydrate, generally is found to be unstable with respect to the starting carbonyl compound and water. Thus, in most cases the hydrate cannot be isolated. However, its existence is deduced from the fact that rapid oxygen exchange is observed: in the presence of ^{18}O enriched water and base, ^{18}O is incorporated rapidly into the carbonyl oxygen of the aldehyde or ketone. This process, which is inferred to occur via the tetrahedral, doubly oxygenated hydrate intermediate, results in randomization of the oxygen atoms in the system, whether they came to the system originally from the carbonyl group or from water.

We immediately should consider the parallel situation in acid [2]. In acid solution the hydrate forms rapidly as well; once again it generally is unstable with respect to the carbonyl compound and water, and its presence is indicated by oxygen exchange, in this case initiated by protonation of the carbonyl oxygen atom. The parallelism of the steps in the base- and the acid-catalyzed cases should be studied carefully. In the base-catalyzed version the strong base hydroxide anion attacks a relatively weak acceptor — the unactivated carbonyl group. In acid one is working with a much weaker base — water — but in compensation the water has the opportunity to attack an activated carbonyl group with heightened acidity (electrophilicity): in essence, an electron sink, in the form of a full positive charge, has been provided. Finally, whereas the last step in base is the *donation* of a proton to the oxyanion by the strongest *acid* available in the basic solution — water, in the case of acid the last step is the *loss* of a proton from the protonated species to the strongest *base* available in the acid solution — water.

As has been previously intimated (see, for example, Segment 16.01), the "dream reaction" would be the one of line [3]. As written, this is not a tenable prospect, for what is in effect a high concentration of protons in conjunction with a high concentration of hydroxide ions is not an allowed condition in aqueous solution. However, in an enzyme cavity exactly this sort of condition can be achieved *on a local basis* [4], leading in turn to the great rate enhancements that enzymes can provide.