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THE OXIBASE SCALE. THE NUCLEOPHILICITIES OF ENOLATE ANIONS IN PROTONIC SOLVENTS[1]

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In earlier papers, the oxibase scale[3,4] has been developed[5] and extended to allow quantitative correlations of structure and reactivity. The simple rules of prediction are based upon the ease of oxidation and the basicity of the nucleophile; and the ease of reduction and the acidity of substrate. In quantitative terms, the oxibase scale is:

$$\log k/k_o = \alpha E + \beta H \qquad (1)$$

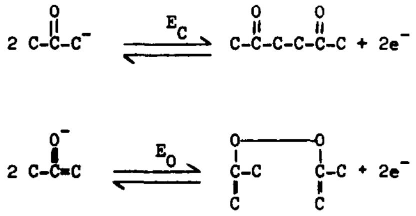
where $\underline{k}$ is the rate constant, $\underline{k_o}$ is the rate constant with a standard nucleophile (water), $\underline{E}$ is the oxidative dimerization potential of the nucleophile relative to water, $\underline{H}$ is the pKa of the nucleophile relative to water; and $\underline{\alpha}$ is the reduction constant of the substrate, and $\underline{\beta}$ is the acidity constant of the substrate, all in water at 25°.

In this note the qualitative applications of these ideas are made to the problem of C-alkylation, O-alkylation, C-acylation and O-acylation of enolate anions. The literature is nicely reviewed by House.[6]

The generalities of the literature can be summarized. C-methylation is favored with methyl iodide but decreases somewhat with methyl sulfate. Very little O-methylation is observed with the usual methylating agents.

O-Acylation is generally favored kinetically over C-acylation.

The enolate anion can be expressed in two extreme forms. One can estimate that the oxidative dimerization potential ought to be larger for the C$^-$ than the O$^-$ because the free energy of the diketone would indicate that it is much more stable than the divinylperoxide.



$$2\ \mathrm{C{-}\overset{\overset{O}{\|}}{C}{-}C^-}\ \overset{E_C}{\rightleftharpoons}\ \mathrm{C{-}\overset{\overset{O}{\|}}{C}{-}C{-}C{-}\overset{\overset{O}{\|}}{C}{-}C} + 2e^-$$

$$2\ \mathrm{C{-}\overset{\overset{O^-}{|}}{C}{=}C}\ \overset{E_O}{\rightleftharpoons}\ \mathrm{\underset{\underset{C}{\|}}{\overset{\overset{O}{|}}{C}}{-}C\quad \underset{\underset{C}{\|}}{\overset{\overset{O}{|}}{C}}{-}C}\ (\mathrm{O{-}O}) + 2e^-$$

Thus $E_C > E_O$

Similar equations could be written for the enols of acetylacetone and other more acidic ketones.

The pKa (or $\underline{H} = \underline{\mathrm{pKa}} + 1.74$) of the C$^-$ would be much lower than the $\underline{H}$ of O$^-$. This is observed in the fact that proton transfer to the O$^-$ anions of enolates is about 10,000 times faster than transfer to the C$^-$ anion[7]. For example, the rate of proton transfer on to the oxygen of acetylacetone anion occurs at a rate of $3 \times 10^{10}\ M^{-1}sec^{-1}$ while the rate constant for protonation on the carbon is $1.2 \times 10^7\ M^{-1}\ sec^{-1}$. Thermodynamics arguments based on the stability of the enolate, the enol and the ketone also show that the $\underline{pK_a}$ of the O$^-$ is larger than that of the C$^-$, even for acetone. Thus using the oxibase scale, the O$^-$ anion is a better base than the C$^-$ anion. Thus the relative orders of the nucleophilic constants can be estimated.

$$H_O > H_C$$

The substrate parameters (α and β) are controlled by the potential of the legate ion (for α)[3] and the electronegativity difference (for β)[4]. The E values[4,5] of the legate ions (leaving groups) are I^- (2.06 volts), Br^- (1.51), Cl^- (1.24), CH_3COO^- (0.94), SO_4^{-2} (0.6), $(CH_3O)_2P(O)O^-$ (0.62), and $^-OSO_2C_6H_4$-CH_3 (0.5). For the methyl derivatives of the strong acids, α decreases linearly with the E value of the legate ion.[3]

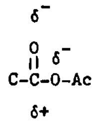
The α of methyl iodide is high (2.98) because the E of the legate is high. The α of methyl tosylate is lower (1.5) and this substrate does not discrimate as much with nucleophiles as does methyl iodide.

·The β values are controlled by the difference in electronegativity. β is a measure of the amount of positive charge at the electrophilic center. The β of methyl iodide is low (nearly zero)[3,4] because carbon and iodine have nearly the same electronegativity.

Now consider the reaction of acetylacetone or the acetoacetic ester with methyl iodide in water. With methyl iodide C-methylation will be observed since it is a reaction controlled by the large E term. The carbon alkylation is controlled kinetically by the oxidation-reduction term.

C^- anion	CH_3I		Result	
E_C large	α large	⟵	C-CH_3	αE large
H_C small	β small			
O^- anion				
E_O small	α large			
H_O large	β small			

Acetic Anhydride has a very poor nucleophile (acetate) as a leaving group and the α is very low. However the polarity difference indicates



$$C-\underset{\delta+}{\overset{\overset{\delta^-}{\overset{O}{\|}}}{C}}-\overset{\delta^-}{O}-Ac$$

that the carbonyl carbon atom is very positive, so β is large. Thus the acylation reaction is controlled by the H term or the acidity-basicity term.

O^- Anion	Ac_2O		Result	
E_O small	α small		O-Ac	βH large
H_O large	β large	←		
C^- Anion				
E_C large	α small			
H_C small	β large			

Several predictions can be made using the oxibase scale for reactions in water or alcoholic solvents since E and H values are known in these systems.

The ratio of C-methylation to O-methylation ought to increase in the series: methyl tosylate, trimethyl phosphate, methyl sulfate, methyl chloride, methyl bromide and methyl iodide. The α of each substrate increases in the order shown.

The ratio of O-acetylation to C-acetylation ought to increase in the series: CH_3COI, bromide, chloride and acetic anhydride. The degree of positive charge on the carbonyl carbon increases in the series shown as the square of the difference of the electronegativities increases in the same order. Unfortunately the E values of legates as R_3N or R_2O are not known to allow prediction in either series. Since the reactions occur in polar protic solvents cation effects would be small.

These simple rules and observations should be great help in the synthesis of complex organic molecules with numerous functional groups or sites. It is a basic hypothesis of the use of the oxibase scale that the examination of the site potentials (E and H or α and β) can be simply made. Further work on the potentials in other solvents is underway.[8,9]

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8. The only other theory that can make only qualitative predictions about reactivity is the "soft-hard acid-base" theory. R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963). However, Hudson (R. F. Hudson, *Structure and Mechanism in Organo-Phosphorus Chemistry*, Academic Press, London, 1965, pp. 126-127, 116-119) states that the limitations of the SHAB concept is clearly seen when ambident ions are considered. The predictions are in error in numerous cases. This critique justifies the present note since the oxibase scale is very quantitative and does quite well in predicting relative free energy differences. The oxibase scale can give a quantitative value to how hard (and what type of hardness) and how soft.
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