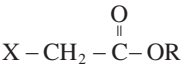
of the biological phase appears to be similar to that of octanol; partitioning of a compound from water into octanol would require complete desolvation of the compound. For some of the examples of QSAR with a slope less than one, the measured effect is a result of binding of ligands to proteins or DNA.

While most of the QSAR observations involve linear relationships between log *P* and toxicity, there are other relationships, such as parabolic, seen between biological response and hydrophobicity. One interpretation to account for this observation is that many membranes may have to be traversed for compounds to get to the target site, and compounds with the greatest hydrophobicity will become localized in the membranes they encounter initially, thereby slowing their transit to the target site.

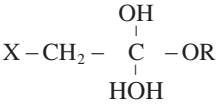
Another factor that alters QSAR involves steric effects. For studies that involve reactivity of organic compounds, a steric parameter, E_s, was defined by Taft as:

$$E_s = \log\left(\frac{K_x}{K_H}\right)_A \tag{4.51}$$

where *k* is the rate constant for the acid hydrolysis of esters of the type:



The transition state for this hydrolysis can be represented as:



Assuming that the electronic effects of substituent X can be ignored, the size of X will affect the transition state and, hence, the rate of the reaction. By definition, $E_s = 0$ for X = H. Table 4.3 lists values of E_s for other substituents.

Another parameter related to molecular volume and steric effects is the molar refractivity (MR). Experimentally, it is obtained from the equation:

$$\mathrm{MR} = \frac{n^2 - 1}{n^2 + 2} \cdot \frac{\mathrm{MW}}{d} \tag{4.52}$$

where *n* is the index of refraction, *d* is the density, and MW is the molecular weight.

Steric effects can be particularly difficult to define in complex biological systems. Quantitative structure–activity relationships in biological systems have been developed by using parameters such as E_s and MR. In addition, factors such as van der Waals radii, standard bond angles and lengths, and conformational flexibility have been applied as a way to define the space occupied by molecules. However, it is often difficult to define a single parameter that can account for all these factors. A more recent treatment of steric effects that is applied to biological systems is the comparative molecular field analysis (CoMFA). This approach, which examines and superimposes the conformations of molecules of interest, is an extension of the ligand-based drug design.