para substituents and the vacant p-orbital in the transition state, which led to deviations in the Hammett plot (85). They defined a modified LFER applicable to this situation.

$$\text{Log}\frac{k_Y}{k_H} = (\rho^+)(\sigma^+) \qquad (1.35)$$

σ^+ was a new substituent constant that expressed enhanced resonance attributes. A similar situation was noticed when a strong donor center was present as a reactant or formed as a product (e.g., phenols and anilines). In this case, strong resonance interactions were possible with electron-withdrawing groups (e.g., NO, or CN). A scale for such substituents was constructed such that

$$\text{Log}\frac{k_Y}{k_H} = (\rho^-)(\sigma^-) \qquad (1.36)$$

One shortcoming of the benzoic acid system is the extent of coupling between the carboxyl group and certain lone-pair donors. Insertion of a methylene group between the core (benzene ring) and the functional group (COOH moiety) leads to phenylacetic acids and the establishment of σ^0 scale from the ionization of X-phenylacetic acids. A flexible method of dealing with the variability of the resonance contribution to the overall electronic demand of a reaction is embodied in the Yukawa-Tsuno equation (86). It includes normal and enhanced resonance contributions to an LFER.

$$\text{Log}\frac{k_Y}{k_H} = \rho[\sigma + r(\sigma^+ - \text{a})] \qquad (1.37)$$

where r is a measure of the degree of enhanced resonance interaction in relation to benzoic acid dissociations ($r = 0$) and cumyl chloride hydrolysis ($r = 1$).

Most of the Hammett-type constants pertain to aromatic systems. In evaluating an electronic parameter for use in aliphatic systems, Taft used the relative acid and base hydrolysis rates for esters. He developed equation 1.38 as a measure of the inductive effect (a*) of a substituent R' in the ester R' COOR, where B and A refer to basic and acidic hydrolysis, respectively.

$$\sigma^* = \frac{1}{2.48}[\log(k/k_O)_B - \log(k/k_O)_A] \qquad (1.38)$$

The factor of 2.48 was used to make a* equiscalar with Hammett a values. Later, a σ_I scale derived from the ionization of 4-X-bicyclo[2.2.2]octane-1-carboxylic acids was shown to be related to a* (87, 88). It is now more widely used than a*.

$$\sigma_I(\text{X}) = 0.45\sigma^*(\text{CH}_2\text{X}) \qquad (1.39)$$

Ionization is a function of the electronic structure of an organic drug molecule. Albert was the first to clearly delineate the relationship between ionization and biological activity (89). Now, pK_a values are widely used as the independent variable in physical organic reactions and in biological systems, particularly when dealing with transport phenomena. However, caution must be exercised in interpreting the dependency of biological activity on pK_a values because pK_a values are inherently composites of electronic factors that are used directly in QSAR analysis.

In recent years, there has been a rapid growth in the application of quantum chemical methodology to QSAR, by direct derivation of electronic descriptors from the molecular wave functions (90). The two most popular methods used for the calculation of quantum chemical descriptors are *ab initio* (Hartree-Fock) and semiempirical methods. As in other electronic parameters, QSAR models incorporating quantum chemical descriptors will include information on the nature of the intermolecular forces involved in the biological response. Unlike other electronic descriptors, there is no statistical error in quantum chemical computations. The errors are usually made in the assumptions that are established to facilitate calculation (91). Quantum chemical descriptors such as net atomic changes, highest occupied molecular orbital/lowest unoccupied molecular orbital (HOMO-LUMO) energies, frontier orbital electron densities, and superdelocalizabilities have been shown