neutral and weakly acidic and basic drugs, revealed an excellent correlation between $\log P_{oct}$ and $\log K_W$ values (129). Log P_{oct} values determined in this system are referred to as Elog P_{oct}. They were expressed in terms of solvation parameters.

$$\begin{aligned} \text{Elog}\,P_{oct} &= 0.204 + 0.452R_2 \\ &\quad - 1.053\pi_2^{H} - 0.041 \sum \alpha_2^{H} \qquad (1.46) \\ &\quad - 3.410 \sum \beta_2^{O} + 3.842V_X \\ n = 35, &\quad r^2 = 0.960, \quad s = 0.244 \end{aligned}$$

In this equation, R, is the excess molar refraction; π_2^H is the dipolarity/polarizability; $\Sigma\, \alpha_2^H$ and $\Sigma\, \beta_2^O$ are the summation of hydrogen bond acidity and basicity values, respectively; and V_X is McGowan's volume.

3.2.2 Calculation Methods. Partition coefficients are additive-constitutive, free energy-related properties. Log P represents the overall hydrophobicity of a molecule, which includes the sum of the hydrophobic contributions of the "parent" molecule and its substituent. Thus, the π value for a substituent may be defined as

$$\pi_X = \log P_{R-X} - \log P_{R-H} \qquad (1.47)$$

π_H is set to zero. The π-value for a nitro substituent is calculated from the log P of nitrobenzene and benzene.

$$\begin{aligned} \pi_{NO_2} &= \log P_{\text{nitrobenzene}} - \log P_{\text{benzene}} \\ &= 1.85 - 2.13 = -0.28 \end{aligned}$$

An extensive list of T-values for aromatic substituents appears in Table 1.4. Pi values for side chains of amino acids in peptides have been well characterized and are easily available (130–132). Aliphatic fragments values were developed a few years later. For a more extensive list of substituent value constants, refer to the extensive compilation by Hansch et al. (133). Initially, the T-system was applied only to substitution on aromatic rings and when the hydrogen being replaced was of innocuous character. It was apparent from the beginning that not all hydrogens on aromatic systems could be substituted without correction factors because of strong electronic interactions. It became necessary to determine π values in various electron-rich and -deficient systems (e.g., X-phenols and X-nitrobenzenes). Correction factors were introduced for special features such as unsaturation, branching, and ring fusion. The proliferation of T-scales made it difficult to ascertain which system was more appropriate for usage, particularly with complex structures.

The shortcomings of this approach provided the impetus for Nys and Rekker to design the fragmental method, a "reductionist" approach, which was based on the statistical analysis of a large number of measured partition coefficients and the subsequent assignment of appropriate values for particular molecular fragments (118, 134). Hansch and Leo took a "constructionist" approach and developed a fragmental system that included correction factors for bonds and proximity effects (1, 135). Labor-intensive efforts and inconsistency in manual calculations were eliminated with the debut of the automated system CLOGP and its powerful SMILES notation (136–138). Recent analysis of the accuracy of CLOGP yielded Equation 1.48 (139).

$$\text{MLOGP} = 0.959\ \text{CLOGP} + 0.08 \qquad (1.48)$$

$$n = 12{,}107, \quad r^2 = 0.973, \quad s = 0.299$$

The Clog P values of 228 structures (1.8% of the data set) were not well predicted. It must be noted that Starlist (most accurate values in the database) contains almost 300 charged nitrogen solutes (ammonium, pyridinium, imidazolium, etc.) and over 2200 in all, which amounts to 5% of Masterfile (database of measured values). CLOGP adequately handles these molecules within the 0.30 standard deviation limit. Most other programs make no attempt to calculate them. For more details on calculating $\log P_{oct}$ from structures, see excellent reviews by Leo (140, 141).

The proliferation of methodologies and programs to calculate partition coefficients continues unabated. These programs are based on substructure approaches or whole-molecule approaches (142, 143). Substructure