to correlate well with various biological activities (92). A mixed approach using frontier orbital theory and topological parameters have been used to calculate Hammett-like substituent constants (93).

$$\begin{aligned}\sigma = {} & -2.480\Delta N - 7.894\Delta E \\ & - 0.605 D_X/D_H \cdot (EA_H/EA_X) \qquad (1.40) \\ & + 0.009\, \O S_X + 0.028 \sum \pi + 0.279 \\ & n = 150, \quad r^2 = 0.947, \\ & s = 0.079, \quad F = 789.9\end{aligned}$$

In Equation 1.40, AN represents the extent of electron transfer between interacting acid-base systems; AE is the energy decrease in bimolecular systems underlying electron transfer; D_X/D_H • (EA_H/EA_X) corresponds to electron affinity and distance terms; and $\O S_X$ factors the electrotopological state index, whereas Σ a is the number of all π-electrons in the functional group. Observed principal component analysis (PCA) clustering of 66 descriptors derived from AM1 calculations was similar to that previously reported for monosubstituted benzenes (94, 95). The advantages of quantum chemical descriptors are that they have definite meaning and are useful in the elucidation of intra- and intermolecular interactions and can easily be derived from the theoretical structure of the molecule.

3.2 Hydrophobicity Parameters

More than a hundred years ago, Meyer and Overton made their seminal discovery on the correlation between oil/water partition coefficients and the narcotic potencies of small organic molecules (7, 8). Ferguson extended this analysis by placing the relationship between depressant action and hydrophobicity in a thermodynamic context; the relative saturation of the depressant in the biophase was a critical determinant of its narcotic potency (9). At this time, the success of the Hammett equation began to permeate structure-activity studies and hydrophobicity as a determinant was relegated to the background. In a landmark study, Hansch and his colleagues devised and used a multiparameter approach that included both electronic and hydrophobic terms, to establish a QSAR for a series of plant growth regulators (16). This study laid the basis for the development of the QSAR paradigm and also firmly established the importance of lipophilicity in biosystems. Over the last 40 years, no other parameter used in QSAR has generated more interest, excitement, and controversy than hydrophobicity (96). Hydrophobic interactions are of critical importance in many areas of chemistry. These include enzyme-ligand interactions, the assembly of lipids in biomembranes, aggregation of surfactants, coagulation, and detergency (97–100). The integrity of biomembranes and the tertiary structure of proteins in solution are determined by apolar-type interactions.

Molecular recognition depends strongly on hydrophobic interactions between ligands and receptors. Excellent treatises on this subject have been written by Taylor (101) and Blokzijl and Engerts (51). Despite extensive usage of the term hydrophobic bond, it is well known that there is no strong attractive force between apolar molecules (102). Frank and Evans were the first to apply a thermodynamic treatment to the solvation of apolar molecules in water at room temperature (103). Their "iceberg" model suggested that a large entropic loss ensued after the dissolution of apolar compounds and the increased structure of water molecules in the surrounding apolar solute. The quantitation of this model led to the development of the "flickering" cluster model of Némethy and Scheraga, which emphasized the formation of hydrogen bonds in liquid water (104). The classical model for hydrophobic interactions was delineated by Kauzmann to describe the van der Waals attractions between the nonpolar parts of two molecules immersed in water. Given that van der Waals forces operate over short distances, the water molecules are squeezed out in the vicinity of the mutually bound apolar surfaces (49). The driving force for this behavior is not that alkanes "hate" water, but rather water that "hates" alkanes (105, 106). Thus, the gain in entropy appears as the critical driving force for hydrophobic interactions that are primarily governed by the repulsion of hydrophobic