were used in addition to **Taft's** E_S values and Swain-Lupton field constants F_{ortho}.

The reason for employing alternative treatments to ortho-substituted aromatic molecules is that changes in rate or ionization constants mediated by meta or para substituents are mostly changes in ($H^{\ddagger}$ or ΔH° because substitution does not affect AS* or AS". **Ortho** substituents affect both enthalpy and entropy; the effect on entropy is noteworthy because entropy is highly sensitive to changes in the size of reagents and substituents as well as degree of solvation. **Bolton** et al. examined the ionization of substituted benzoic acids and measured accurate values for AG, AH, and A S (81). **A** hierarchy of different scenarios, under which an LFER operates, was established:

1. ΔH° is constant and A S varies for a series.
2. AS" is constant and AH varies.
3. ΔH° and AS" vary and are shown to be linearly related.
4. Precise measurements indicated that category 3 was the prevalent behavior in **benzoic** acids.

Despite the extensive and successful use in QSAR studies, there are some limitations to the Hammett equation.

1. Primary a values are obtained from the thermodynamic ionizations of the appropriate benzoic acids at 25°C; these are reliable and easily available. Secondary values are obtained by comparison with another series of compounds and are thus subject to error because they are dependent on the accuracy of a measured series and the development of a regression line using statistical methods.
2. In some multisubstituted compounds, the lack of additivity needs to be noted. Proximal effects are operative and tend to distort electronic contributions. For example,

$$\sum \sigma_{\text{calc}}(\text{3,4,5-trichlorobenzoic acid}) = 0.97;$$

$$\text{that is, } 2\sigma_{\text{M}} + \sigma_{\text{P}} \quad \text{or} \quad 2(0.37) + 0.23$$

$$\sum \sigma_{\text{obs}}(\text{3,4,5-trichlorobenzoic acid}) = 0.95$$

Sigma values for smaller substituents are more likely to be additive. However, in the case of 3-methyl, 4-dimethylaminobenzoic acid, the discrepancy is high. For example,

$$\sum \sigma_{\text{calc}}(\text{3-CH}_3\text{, 4-N(CH}_3)_2 \text{ benzoic acid}) = -0.90$$

$$\sum \sigma_{\text{obs}}(\text{3-CH}_3\text{, 4-N(CH}_3)_2 \text{ benzoic acid}) = -0.30$$

The large discrepancy may be attributed to the twisting of the dimethylamino **substituent** out of the plane of the benzene ring, resulting in a decrease in resonance. Exner and his colleagues have critically examined the use of additivity in the determination of a constants (82).

3. Changes in mechanism or transition state cause discontinuities in Hammett plots. Nonlinear plots are often found in reactions that proceed by two concurrent pathways (83, 84).
4. Changes in solvent may lead to dissimilarities in reaction mechanisms. Thus extrapolation of σ values from a polar **solvent** (e.g., CH_3CN) to a nonpolar solvent such as benzene has to be approached cautiously. Solvation properties will differ considerably, particularly if the transition state is polar **and/or** the substituents are able to interact with the solvent.
5. **A** strong positional dependency of sigma makes it imperative to use appropriate values for positional, isomeric substituents. Substituents **ortho** to the reaction center are difficult to describe and thus one must resort to a Fujita-Nishioka analysis (80).
6. Thorough resonance or direct conjugation effects cause a breakdown in the Hammett equation. When coupling occurs between the substituent and the reaction center through the pi-electron system, reactivity is enhanced, diminished, or mitigated by separation. In a study of X-cumyl chlorides, Brown and Okamoto noticed the strong conjugative interaction between lone-pair,