This Week’s Citation Classic


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When I started my research career at Kyoto in 1951, I selected a project in structure-activity relationships of plant growth regulators. My special concern was how to rationalize the fact that some regulators were very potent but other closely related analogs were not. I tried to approach this problem in terms of physicochemical parameters of the molecule. I determined the hydrophilic/lipophilic balance by a polarographic procedure, analyzed three-dimensional structures by their spectra and dipole moments, and calculated the electronic parameters using the molecular orbital (MO) method. These parameters were capable of rationalizing the activity if used singly only when other parameters were kept nearly constant in a set of compounds. A multiple-parameter approach was apparently needed, although I did not know how to do it at that time.

For the MO calculation, I asked the advice of Kenichi Fukui, a Nobel Prize winner, and his associate, Chikayoshi Nagata. In fact, they had analyzed the plant-growth activity data of substituted benzoic acid derivatives by their spectra and dipole moments, and calculated the electronic parameters in QSAR. It has been noticed that the log P value of compounds was found to be additive and constitutive, being composed of log P of the parent compound and π values of substituents with electronic and steric corrections for intramolecular interactions.

One of the reasons for the paper being cited so often is that π is one of the most important parameters in QSAR. It has been widely used to analyze substituent effects along with the electronic parameter ω and such a steric parameter as E° in quantitative-structure-activity studies of diverse drugs and agrochemicals. The first QSAR paper was published in 1962. The prediction of the log P value has become extremely important in the assessment of environmental accumulation of organic chemicals. Currently, a computerized procedure for predicting log P has been developed in Pomona.

This paper presents the nature and composition of the π parameter in a number of aromatic systems showing that the value is a constant assignable to each substituent but dependent to some extent on electronic interactions with a substituent already located on the aromatic ring. (The SCF® indicates that this paper has been cited in over 760 publications.)