

Fujita T, Iwasa J & Hansch C. A new substituent constant,  $\pi$ , derived from partition coefficients. *J. Amer. Chem. Soc.* 86:5175-80, 1964.  
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This paper presents the nature and composition of the  $\pi$  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 *SC*<sup>®</sup> indicates that this paper has been cited in over 780 publications.]

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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 acids, published by Hansch and Muir,<sup>1</sup> using their "frontier electron" theory.<sup>2</sup> This theoretical work supported a hypothesis for the action mechanism put forward by Hansch. Thus, when Hansch inquired of Fukui about someone who could work as a postdoc at Pomona, he recommended me.

Thanks to Fukui's kind arrangement, I joined Corwin Hansch in 1961 when he had just started to de-

velop a new model for structure-activity correlation using more than one variable. I was very lucky to participate in this project, since it showed me how to materialize the multiparameter procedure. Hansch decided to use the partition coefficient (P) as a parameter for penetration of the plant growth regulators to their site of action in cells. My first job was to determine the P value of a number of substituted phenoxycetic acids in an octanol/water system. We soon recognized that the log P value works nicely in correlating the growth activity of phenoxycetic acids. As the substituent parameter, we defined  $\pi$  as  $\log P_X - \log P_H$  in a manner similar to the Hammett  $\sigma$  electronic substituent parameter. Using  $\sigma$  and  $\pi$  as the independent variables, we established a quantitative model to analyze structure-activity relationships. We soon found that the model can apply to diverse drugs and agrochemicals, which resulted in the development of "Quantitative Structure-Activity Relationship (QSAR)—The Hansch Approach." We published two papers consecutively on the QSAR of plant growth regulators<sup>3</sup> and other bioactive compounds.<sup>4</sup> The article that became a *Citation Classic* was published as the third of the series, since we wanted to demonstrate first the versatility of the QSAR procedure and then to illustrate the nature and composition of the  $\pi$  value, which had already been shown to be very useful in QSAR. The log P value of compounds was found to be additive and constitutive, being composed of log P of the parent compound and  $\pi$  values of substituents with electronic and steric corrections for intramolecular interactions.<sup>5,6</sup>

One of the reasons for the paper being cited so often is that the  $\pi$  is one of the most important parameters in QSAR. It has been widely used to analyze substituent effects along with the substituent electronic parameter  $\sigma$  and such a steric parameter as  $E_s$  in quantitative-structure-activity studies of diverse drugs and agrochemicals. The second QSAR paper<sup>4</sup> was nominated as a *Citation Classic* in 1982. The prediction of the log P value has become extremely important in the assessment of environmental accumulation of organic chemicals. Recently, a computerized procedure for predicting log P has been developed in Pomona.<sup>7</sup>

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