

Hansch C & Fujita T.  $\rho$ - $\sigma$ - $\pi$  analysis. A method for the correlation of biological activity and chemical structure.

*J. Amer. Chem. Soc.* 86:1616-26, 1964.

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This paper presents a mathematical model which correlates the differences in physico-chemical properties of a set of organic compounds produced in biochemical and biological systems. It shows that systems as diverse as benzoic acids inhibiting mosquito larvae, phenols inhibiting bacteria, phosphate esters killing houseflies, the analgesic action of diethylaminoethyl benzoates on guinea pigs, the action of thyroxine analogs on rodents, and the carcinogenicity of polycyclic aromatic hydrocarbons could be correlated with two parameters—the Hammett  $\rho$  constant and a hydrophobicity parameter derived from octanol/water partition coefficients. [The SCI® indicates that this paper has been cited in over 535 publications since 1964.]

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"On coming to Pomona College in 1946, I soon became acquainted with and joined forces with Robert Muir, a plant physiologist in the botany department, in an attempt to understand how changes in chemical structure affected the potency of plant growth-regulators. Shortly thereafter Muir moved to the University of Iowa where he remains today. At that time, Muir was among the relative few who appreciated that the phenoxyacetic acids probably acted by the same mechanism as the natural growth hormone indoleacetic acid. The indole compounds were hard to synthesize while the phenoxyacetic acids were easy to make. Together, we

systematically studied the action of phenoxyacetic acids on oat seedlings.

"We developed qualitative ideas about the relationship of chemical structure and biological activity, trying to explain in terms of one variable the electron distribution in the phenoxy ring. Around 1960 it became clear that this simplistic approach was worthless, even as an approximation. Several variables were obviously involved and their separate roles had to be delineated. We decided to use partition coefficients (the way a compound distributes itself between an oily phase and water) to model the way the growth-regulators penetrate to their sites of action in cells. Just as our model was developing, Toshio Fujita, a chemist from Kyoto University, joined us to help, and at about that same time an alumnus of the college gave our department a small computer. Being a synthetic organic chemist, I had never in my life expected to use a computer and probably would not have done so without the help of Donald McIntyre, a Pomona geologist. We published our first paper on quantitative structure-activity relationships (this has now developed into a field called QSAR) in 1962.<sup>1</sup> Fujita and I then went on to apply our mathematical model using numbers to describe the partitioning, spatial, and electronic properties of organic compounds, which resulted in this *Citation Classic*.

"The reason for the paper being cited so often is that this was the first quasi-general mathematical approach to structure-activity relationships. Today our approach has been shown to be valuable in drug and pesticide design, toxicology, reaction of organic compounds with enzymes<sup>2</sup> and other macromolecules, disposition of chemicals in soil, and the bioaccumulation of environmental chemicals in fish, birds, and other forms of life."

1. Hansch C, Moloney P P, Fujita T & Muir R M. Correlation of biological activity with Hammett substituent constants and partition coefficients. *Nature* 194:178-80, 1962.
2. Smith R N, Hansch C, Kim K H, Oulys B, Fokunson G, Schenck C D, Jew P Y C, Blaney J B & Langridge R. The use of crystallography, graphics, and quantitative structure-activity relationships in the analysis of the papain hydrolysis of X-phenyl hippuronates. *Arch. Biochem. Biophys.* 215:319-26, 1982.