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This Week's Citation Classic

Leo A, Hansch C & Elkins D. Partition coefficients and their uses.
Chem. Rev. **71**:525-616, 1971.
[Dept. Chemistry, Pomona College, Claremont, CA]

The equilibrium of a solute between a lipid and an aqueous phase has been investigated systematically beginning with Berthelot in 1872,[1] and was put on a firm basis by Nernst in 1891.[2] Not all the pertinent literature since that time could be included in this review, but attention is paid to the application of Henry's law and to nonideal solute behavior, especially ionization and dimerization. Application to current problems in biological structure-activity is stressed, and over 5,800 partition coefficients are listed. [The *SCI*® indicates that this paper has been cited in over 945 publications since 1971.]

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"Occasionally in the field of science, a new procedure or technique is developed, enjoys some success, but then gradually becomes neglected by the scientific community until a new need arises, whereupon its revived success far exceeds that achieved earlier. The partition coefficient, which measures a physicochemical property called hydrophobicity, saw such a resurgence of interest in the last 15 years, and I feel very fortunate indeed to have been in the right place at the right time to take a part in it. The 'right place' was the research group headed by Corwin Hansch at Pomona College who were using regression analysis and Hammett's[3] 'extrathermodynamic' parameters to quantitate biological activity with structure. By 1969, these methods, using conventional electronic and steric parameters, proved very useful in predicting rates and equilibria of reactions *in vitro*—even those involving enzyme inhibition which were known to be critical in producing the overall observed biological endpoint. But until Hansch and Fujita[4] established the additive-constituitive nature of the hydrophobic parameter and showed that it could quantify the transport factor, drug and pesticide design, for example, was more intuitive than rational.

"To me, the fact that this review article became a *Citation Classic* has some important lessons for those in the scientific community who, like myself, seemed headed for quiet oblivion. After receiving my PhD from the University of Chicago in 1952, I spent ten years in applied research and six years in administration. By this time I deeply missed scientific research, but was resigned to the fact that after so long a hiatus there was little chance of my making any original contribution. But the Pomona group needed someone to manage the parametric data being generated in their labs as well as to search and organize the data gathered from the literature. Not surprisingly, for the latter task, the *Science Citation Index*® proved to be invaluable in following up data sources, because much of the partitioning data are not indexed as such. The task of assembling and critically reviewing the partition coefficient data base made it necessary for me to become well informed about its applications and about the solvation forces which compete in the two phases. Writing the review article seemed natural even though my direct contribution to the field was minimal.

"Since 1971, the partition coefficient data base has expanded fourfold and yet the increased demand for values far exceeds the rate at which they are being measured. For this reason we have developed a computer method of calculation from structure, designing it to fit the new generation of microprocessors. The current list of applications[5] for the hydrophobic parameter (log P octanol:water) is twice that of 1971: drug and pesticide design, pharmacokinetics, anaesthesiology, environmental transport and soil binding, toxicology, bioaccumulation, protein folding, enzyme binding, enzymic reactions in nonaqueous solvents, and host-guest complexation. Undoubtedly, a primary reason this article was so frequently cited was that it contained the most comprehensive list of the hydrophobic parameters which are useful in all these fields.

"In recognition of the effort of designing a method of calculating log P (o:w) from structure, the early version of which was reported in this article, the Chesapeake section of Sigma Xi presented me with its Excellence in Science Award for 1980."

1. **Berthelot M & Jungfleisch E.** *Ann. Chim. Phys.* **4**:26, 1872.
2. **Nernst W.** *Z. Phys. Chem.* **8**:110, 1891.
3. **Hammett L P.** *Physical organic chemistry*. New York: McGraw Hill, 1970. 420 p.
4. **Hansch C & Fujita T.** ρ-σ-π analysis. A method for the correlation of biological activity and chemical structure. *J. Amer. Chem. Soc.* **86**:1616-26, 1964.
[Citation Classic. *Current Contents/Life Sciences* **25**(47):18, 22 November 1982.]
5. **Leo A.** The octanol/water partition coefficients of aromatic solutes: the effect of electronic interactions, alkyl chains, hydrogen bonds and ortho substitution. *J. Chem. Soc. Perkin Trans. II.* In press, 1983.