CC/NUMBER 20
MAY 17. 1993

This Week's Citation Classic

Rekker R F. *The Indrophobic fragmental constant: its derivation and application with a means of characterizing membrane systems.* Amsterdam. The Netherlands: Elsevier. 1977. 390 p. [Gist—Brocades Research and Development Department. Haarlem. The Netherlands]‖

This monograph presents in detail the definition and evaluation of a new approach for the calculation of lipophilicities of organic compounds. The proposed method makes use of fragmenta/constants instead of previously applied *substituent* constants. Its attractiveness is its transparency and its far-reaching applicability in the calculation of lipophilicities in alternative solvent systems. [The *SCI*® indicates that this book has been cited in more than 725 publications.]

The Hydrophobic Fragmental Constant

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My activities in pharmacochemistry began in the late fifties, when I shared my working hours between the teaching of chemistry in the medical faculty of Vrije Universiteit and a research function at "Brocades." In the latter job, heading the physicochemistry group, I got involved very early in studies connected with quantitative structure-activity relationships. Back then the benzhydryl aminoethyl ethers were a favorite project of our group. These ethers displayed at least two distinct pharmacological effects, anthihistaminicandanticholinergic, andwewere a little bit proud of our construction of a hypothetical receptor model suited for attachment of both histamine and a diphenhydramine derivative on three distinct binding sites.[1]

In 1971 I attended C. Hansch's seminar in Paris on "Pharmacologic Activity and Physicochemical Constants." The participants were thoroughly confronted by many aspects of lipophilicity (log P) calculations in the octanol/water partition system.[2] In a private talk with Hansch I told him of some of the latest developments in our antihistamine research, including our receptor modelings. Instead of getting the expected approbation, I was disappointed: From log P studies,[3] Hansch objected, it had become evident that structures like diphenhydramine were to folded (with its electronegative N bending over one of the benzene rings), so that any acceptable receptor model not offering binding facilities to a folded structure ought to be rejected a priori.

A second nasty problem arose between Hansch and me on the simplest conceivable molecule: H_2. Hansch was very surprised by the fact that log P of ethylene glycol could not be obtained by simply doubling the methanol value. My comment that this would imply a log P value of 0.000 for H_2 independent of the applied solvent pair led to a penetrating discussion; the disagreement, however, remained unresolved.

I returned to my research department with far from pleasant feelings and decided to start some studies on octanol/water partition. Our research director of that time—more impressed by log Ps in systems like ox-claw oil/water than in a much less natural-looking system, octanol/water—did not encourage such investigations. Fortunately, I had the privilege to spend 10 percent of my working hours on so-called free-research topics. This meant for me and one of my close collaborators, Gilbert Nys, that we could make a quiet, practically unmonitored start into what turned out to become a successful route. We rejected the Hansch approach of the *substituent* constant (the lipophilicity value of a group or atom when it *substitutes* an H atom in a structure) and introduced our new concept, the hydrophobic *fragmental* constant: the *proper* lipophilicity contribution of a *constituent part of* a structure to the total lipophilicity. We soon became aware of three important facts: (a) the fragmental method allows log P calculations of high accuracy; (b) log P (H_2) in octanol/water - 0.40, in good accord with experiments; (c) folding in the sense of Hansch's proposals does not exist.[4] in addition we got information on the existence of lipophilicity factors operating in fixed multiples of 0.219 (a recently established value) which have due connections with either internal or external hydration phenomena. Application of the fragmental system in alternative partition systems[5] as well as in high pressure liquid chromatography studies seems very promising.

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Received January 19. IW