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PERSPECTIVE

How medicinal chemists learned about log *P*

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Abstract
Although log *P* is now recognized to be a key factor that determines the bioactivity of a molecule, the focus of medicinal chemists on hydrophobicity and log *P* started with the quantitative structure–activity relationships (QSAR) publications of Hansch and Fujita. Their original publication represents a dramatic change of focus to incorporate consideration of log *P* after a decade of work unsuccessfully attempting to use the Hammett equation to explain the structure-activity relationships of plant growth regulators. QSAR allows one to explore the quantitative relationship between log *P* and biological activity even when other factors also influence potency. In particular, Hansch's publications of thousands of QSAR equations demonstrate that a relationship of biological activity with log *P* is indeed a general phenomenon. Hansch's group also provided data and tools that enable others to explore the relationship between log *P* and the biological activity of compounds of interest.

Keywords QSAR · Hydrophobicity · Log *P* · Quantitative structure–activity relationships · Hansch · Fujita · Overton · Meyer · Collander

Hydrophobicity as measured by the 1-octanol/water log *P* affects not only potency, but also absorption, distribution, and toxicity of a molecule to an organism [1–6]. Although it is now recognized to be an important factor in the bioactivity of a molecule, the focus of medicinal chemists on hydrophobicity and log *P* started with the pioneering publications of Hansch and Fujita [7]. In earlier work based on limited datasets, pharmacologists and physiologists postulated a relationship between the tendency of a compound to partition to a non-aqueous phase and a biological property of interest [8–10]. However, for partitioning to become part of scientist's thinking it had to be demonstrated that a relationship to biological activity is indeed a general phenomenon and that it is straightforward for one to use this information in one's own research. This report will argue that the persistent work of Corwin Hansch and his many collaborators are responsible for the current focus on log *P*. His development with Toshio Fujita of quantitative structure–activity relationships (QSAR) provided the tools for the exploration of the quantitative relationship between log *P* and biological activity even when other factors also influence potency [7]. Hansch and collaborators went on to demonstrate the universality of a hydrophobic effect on many biological properties and to provide data and tools that enable others to explore this factor in their own research [11–14].

Early interest in water–oil partitioning

Before the publication of the first QSAR papers, there were many publications that examined the relationship between biological activity and lipid solubility or partitioning. All these studies used measured partition coefficients or other physical properties. Although often a graph was provided, none of the articles examined here reported an equation that relates partition coefficient to biological potency. These studies were performed by pharmacologists, physiologists, or physical chemists. A common feature of many of these publications is that they don't include the structures of the molecules studied, just the name. In fact, in the early 1900s, there were two schools of thought as to what governs the biological activity of a molecule; its chemical structure as such [15] or, indirectly, its physical properties. Physical properties became the predominant theory, but the role of chemical structure per se remained an area of interest [16].

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The observation of the relationship between lipid solubility and biological properties dates back at least to 1863 with the observation that the toxicities of alcohols, ethers, and ketones were inversely correlated with their aqueous solubilities, itself an inverse of partition coefficient [17]. A few years later Meyer [9] and Ernst Overton [8, 18] published on the relationships between lipid/water partition coefficients and anesthetic potency. Overton's extensive studies on partitioning were summarized in a German-language book [18] that is now available in an English translation [19]. The subject remained an active interest of pharmacologists, biochemists, and physical chemists up to the time of the original QSAR publication. For example, in 1949 the biochemist Booij referred to Overton without citation as if his contribution is common knowledge [20].

Physiologists and pharmacologists postulated that because membranes are hydrophobic, in order to transverse a membrane a molecule must itself be hydrophobic. For example, in 1937 Collander reported that the permeability of plant protoplasts to non-electrolytes is correlated with the partition coefficients of the molecules [21]. Similarly, in 1956 Treherne demonstrated a linear correlation between the logarithm of the permeability of non-electrolytes through rabbit skin with the logarithm of the ether-water partition coefficient [22]. Further studies in the late 1950s by Brodie, Schanker and colleagues attributed lipid/water partition coefficients as important contributors to the absorption of the drugs from the gastrointestinal tract and penetration into the cerebrospinal fluid [23–25]. They used chloroform/water and heptane/water as model partitioning systems. Hydrophobicity was also familiar to physical chemists because it is the basis of the surface activity of amphipathic molecules [26].

Starting in the 1940s, H. Veldstra, a Dutch biochemist, postulated that the biological activity of plant growth regulators required the proper balance between the hydrophilic and lipophilic parts of the molecule, HLB [27, 28]. HLB is simply the fraction of the molecule that is hydrophilic. The Veldstra group measured HLB for compounds of interest and found that substituent effects on HLB appear to be transferable and additive. Furthermore, there is an optimum HLB within series that is rather constant from series to series [29]. They interpreted the optimum HLB to mean that lipophilic binding to the cell membrane is necessary for cell penetration, but that if a compound is too lipophilic, it will not move easily into the interior of the cell. It should be noted that none of Veldstra's reports cited the partitioning work of Overton, Meyer, or Collander although Veldstra's collaborator Booij did know of Overton's work [29].

In spite of the above work, in the 1940s and 1950s most medicinal and organic chemists did not consider hydrophobicity or partition coefficients in the design process. However, in a report on a war-time effort, the prominent organic chemist Louis Fieser and colleagues reported the influence of ether-water distribution on the potency of naphthoquinone as antimalarials [30]. In particular, they noted the apparent additivity of substituent effects on the partition coefficient and observed that the optimum partition coefficient is the same for different series of molecules. (Their report can be confusing because they did not report a partition or distribution coefficient, but rather reported pE, the pH of an aqueous buffer at which the concentration of the neutral form in ether is 100× that of the anion in water. Thus, pE is linearly correlated with log P for a series in which pK_a is constant. In spite of this publication, the role of partitioning was absent from the discussions of organic chemists, so it is natural that Hansch and Fujita were unaware of its possible importance.

On a personal note, chemists from Abbott Laboratories were also investigators on the anti-malarial project headed by Fieser [31]. Harold Zaugg, one of these co-authors, was still at Abbott when I started QSAR in 1968. He had no recollection of the partitioning experiments and doubted that it had any influence on Abbott research.

As further evidence of the lack of attention to partitioning in general is the fact that Adrian Albert in the book "Selectivity Toxicity" summarizes a 1954 article that shows that the bacteriostatic action of oximes first rises and then falls with increasing oleyl alcohol/water partition coefficient [32], but does not cite Hansch or Fujita and rather treats this observation as a curiosity [33].

It is worth noting that the paucity of analytical instrumentation meant that measuring partition coefficients was not simple in earlier times. For example in the late 1800s and early 1900s, Overton quantitated the amount of compound in each phase by four methods [19]: For non-volatile compounds he evaporated the solvent and weighed the residue; for volatile compounds that are not soluble in water, he measured the volume of the gas above the solution; and for volatile compounds, he measured the volume increase of each phase. Overton also made use of bioassay methods for quantitation. During the 1930s to the 1950s Collander's methods for quantitation included acid–base titration for ionizable substances, Kjeldahl determination of nitrogen in nitrogen-containing compounds, weighing the residue, and specific bioassay methods [34]. During the 1940s and 1950s Veldstra and colleagues used two methods to measure hydrophilic/lipophilic balance, HLB. In the first, they measured the suppression of the oxygen signal at the dropping mercury electrode. They postulated that mercury is more lipophilic than the water; hence, the more lipophilic a substance, the more strongly it would interact with the mercury [28]. This test was replaced by one in which they measured the ability of compounds to stabilize or destabilize a coacervate of oleate micelles [29]. In the 1940s Fieser's group measured concentrations with colorimetry in the visible region of the spectrum [30]. The availability of the DU UV–Vis spectrophotomer in 1941 meant that it would now be more

straightforward to measure partition coefficients, although it was not until the early 1960s that the Pomona group had access to a spectrophotometer [35].

The role of hydrophobicity in protein structure

During the period when Hansch was struggling to understand the basis of the structure–activity relationships of plant growth inhibitors, biochemists were struggling to understand the forces that stabilize the 3D structure of a protein. A 1959 review by Kauzmann elegantly summarized the evidence that much of this stabilization is due to hydrophobic interactions [36]. This seminal review was widely discussed in the literature, seminars, and informal conversations and led to the immediate acceptance of the important role that hydrophobicity plays in protein stabilization [37]. Protein chemists now realized that the stability of the 3D structure of proteins cannot be explained by the intricate hydrogen bonding shown by the recently discovered α-helixes [38] and β-sheets [39], because hydrogen bonds between residues within a protein structure are perhaps no more stable than hydrogen bonds between the same residues and the water in which the unfolded protein is dissolved [40]. Hence, hydrophobic interactions are considered to account for much of the stability of 3D protein structures. Although it is generally agreed that the hydrophobic effect arises from the strong intramolecular attraction between water molecules, the atomic details leading to the effect remain a mystery [41–43]. It is clear that liquid water is a complex entity with a constantly changing network of hydrogen bonds and that nonpolar substances somehow disrupt this network.

An interesting side-light in view of the sparse recognition of the hydrophobic effect at the time [37], in an 1949 article Booij and Veldstra state "the fact that the driving forces which cause the absorption of the compound into the micelles are not in the first place the London-Van der Waals forces between the non-polar parts of 'agent' and 'substrate', but more probably the mutual forces between the water molecules, an effect which drives a non-polar compound out of solution" [29]. This insight did not suggest to them to use a simple partitioning system to measure lipophilicity, perhaps because there was no convenient method to quantitate the concentration. Booij and Veldstra perhaps had read an earlier discussion of the role of water in micelle formation [44].

The lack of attention by organic chemists in the late 1950s to the newly recognized importance of hydrophobicity perhaps is due to the fact that hydrophobicity results from the very specific properties of liquid water—this not a consideration that is traditional in organic chemistry. Furthermore, in the 1940s and 1950s organic chemists found that the Hammett approach provides a very powerful method to study structure activity relationships [45]. Also in the 1940s and 1950s, prominent biochemists considered that the strength of non-covalent interactions is due to hydrogen bonding [38, 39, 46] and dispersion interactions [47]—hydrophobicity was not considered.

It is worth noting that neither Fieser nor his collaborators expanded their initial observations on the relationship between partition coefficient and bioactivity, but instead returned to studies of organic synthesis. In addition, Pauling continued his focus on 3D structure and never incorporated the idea of hydrophobicity into his thinking [37] even though he was well aware of the structural properties of water [48]. Instead, Pauling proposed that molecules act as anesthetics by forming minute clathrate type hydrate crystals in the brain [49].

Early observations of substituent effects on hydrophobicity

Runar Collander demonstrated that there is a correlation between the 2-methyl-1-propanol and the 1-octanol partition coefficients of compounds [50]. This observation supports the hypothesis that the relative partitioning behavior of a set of molecules is relatively constant, independent of the non-polar phase. Collander's ties to Overton are shown his an extensive obituary praising Overton's work and his contributions to the field of membrane permeability [51]. Collander also found that each methylene group adds a constant amount to log P in a number of series and that other substituents have a reasonably constant effect on partition coefficient [34, 50].

In addition, the Veldstra group found that substituent effects on hydrophilic-lipophilic balance (partitioning) appear to be transferable and additive. The Fieser group also noted the apparent additivity of substituent effects on the partition coefficient [30].

In 1957 Davies suggested a method for calculating HLB that considers the relative hydrophilicity of the nonpolar atoms:

$$\mathrm{HLB} = 7 + \sum_{(i=1)}^{m} H_i - n \times 0.475 \tag{1}$$

in which i is the group number for a hydrophilic group, m is the number of hydrophilic groups, H_i is the hydrophilicity of group i, and n is the number of lipophilic groups [52].

Early studies on plant growth regulators

Hansch and Robert Muir, a plant physiologist who for a time was also a faculty member at Pomona College, started collaborating in 1946 [12]. To probe the structure–activity relationships of phenoxyacetic acid plant growth regulators,

Hansch synthesized analogues or purified purchased compounds and Muir measured their ability to stimulate plant growth.

At this time organic chemists used the Hammett equation, which uses transferable electronic substituent constants to study structure activity relationships in reaction rates or equilibria [45]:

$$\log K = \log K_0 + \rho\sigma \tag{2}$$

in which K is the rate or equilibrium constant of interest, K_0 is the corresponding constant for the unsubstituted compound, ρ is the sensitivity of the reaction to the electronic effect, and σ is the electronic effect of the substituent of interest. Typically σ values are determined by the effect of the substituent on the ionization constant of the parent molecule. Jaffé's review of applications of the Hammett equation [45], a citation classic [53], cites more than 318 references and includes regression equations for 204 different types of organic reactions and equilibria. This intense interest in the Hammett equation spurred further developments of the approach such as the work of Taft on the separation of polar, steric, and resonance effects in reactivity [54]:

$$\log K = \log K_0 + \rho\sigma + cE_s \tag{3}$$

in which E_s is a substituent constant for the steric effect of the substituent. Undoubtedly, the popularity of the Hammett equation profoundly influenced Hansch's initial approach to studying the structure–activity relationships of plant growth inhibitors [55, 56].

In a 1949 report, Hansch and Muir stated "the position on the benzene ring adjacent to the point of attachment of the side chain is directly involved in the growth reaction" [57]. This is based on the biological activity of seven halogen-substituted phenoxyacetic acids. The next year this concept is solidified in a report in which they state "plant growth regulators of the above types react with a plant substrate through an ortho position" [58]. Two 1951 publications expanded the consideration to benzoic acids [59, 60]. The first report proposed a nucleophilic attack by a plant protein on the carbon bearing the chloro substituent. The second report demonstrated the release of chloride ion when 2,6-dichlorobenzoic acid is incubated with plant tissue and proposed that a cysteine SH group is the nucleophile. In an extensive 1953 review [55] again the reactivity hypothesis is argued and "it would seem that knowledge of the hydrophilic/lipophilic ratio would be of little help in predicting or explaining relative activity except in extreme cases". No further publications on plant growth substances appear from this group until the first QSAR publication in 1962, presumably because Hansch was diverted by teaching and working on his organic chemistry workbook, which was published in 1959 [61].

In a retrospective publication, Hansch reported that he was frustrated that with all that work, he still did not understand the basis of the structure–activity relationships of these compounds nor could he predict if a new molecule would be active or not [62]. It was during a sabbatical in the late 1950s that he decided to look into partitioning and found the work by Collander [50, 63].

At the same time, Veldstra, a Dutch biochemist, was also investigating substances that stimulate plant growth [27–29, 64–75]. He postulated a pure non-covalent interaction of the acids with the plant components and argued that that two features of a molecule were essential for it to show activity: (a) the proper spatial relationship between an acidic function and an aromatic ring, and (b) the balance between the hydrophilic and lipophilic parts of the molecule, HLB [27, 28]. As noted above, they found there is an optimum HLB within series and that this optimum is rather constant from series to series suggesting that there is lipophilic binding to the cell membrane, but highly lipophilic compounds do not move easily into the interior of the cell. Veldstra's 1953 review caustically criticized the work of Hansch and Muir [28]. None of their reports cite earlier work on cell penetration [8, 9, 18, 21, 22].

Also at the same time, Toshio Fujita was a graduate student in agricultural chemistry at Kyoto University. In 1952 he and Mitsui published a paper in which they applied Veldstra's polarographic method for HLB determination to naphthoic acid derivatives and other plant growth regulators [76]. They concluded that "the physiological activity of plant growth substance (sic) does not directly depend on the surface activity". However, in 1960 they published a paper in which they revisited the HLB proposal by calculating HLB using the method of Davies [52, 77]. They found that, in agreement with Veldstra's results [28], there is an optimum HLB. Thus, before he went to Pomona College, Fujita was already aware of the power of additive constitutive properties such as they would later use to calculate 1-octanol–water log P and of the idea of an optimum hydrophobicity within a series of molecules.

The Hansch-Muir ortho-reactivity hypothesis of benzoic acids had been supported by quantum chemical calculations by Fukui [78]. Fujita and co-workers extended the calculations to 1-naphthoic acid derivatives [79] and concluded that the hypothesis of a chemical reaction of the compounds with a plant substance cannot be supported, but that instead a non-covalent interaction is indicated. On the other hand, their studies also challenge the Veldstra hypothesis of van der Waals interaction between the aromatic ring and a plant substance, but instead provided evidence for a charge-transfer interaction at specific positions in the aromatic ring. They also noted that the hydrophilic-lipophilic balance seems to affect permeability and diffusibility into the cells.

The invention of QSAR

As well as publishing results of the studies with Muir, Hansch gave a seminar on their work at the California Institute of Technology. Linus Pauling was in the audience. Hansch attributes Pauling's influence when he was awarded an NIH grant in the spurt of increased funding of US science due to the Soviet launching of Sputnik in 1957. Because Pomona College is not a university with a wide range of chemical research, Hansch felt that he would be more likely to attract a Japanese or European post-doctoral fellow than an American one, so he asked Fukui to suggest a Japanese post-doctoral fellow to him [62]. This brought Toshio Fujita to Pomona College.

Just before Fujita arrived, Hansch had decided that partition coefficients might be of interest [56]. An important insight was to not use Vestra's methods for the measurements, but to instead directly measure partitioning between water and a non-aqueous phase. Rejecting the use of olive oil because of its variable composition, Hansch followed the precedent of Collander [50] to have 1-octanol–water partition coefficients measured [62]. Their first measurements quantified concentrations with acid–base titrations.

When Fujita joined the Hansch group, he continued the work of measuring partition coefficients. However, they soon discovered that log P also did not correlate with the potency of the phenoxy acetic acids. Figures 1 and 2 show the results with the data from their first QSAR report [7]. Figure 1 shows the relationship between Hammett σ and potency, a poor relationship. Figure 2 shows the relationship with π, still not convincing.

Fujita suggested that the correlation of potency required a multi-parameter approach, such as that pioneered by Taft

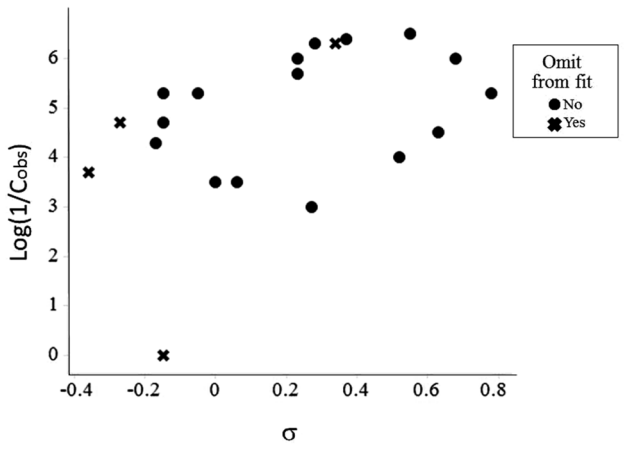

Fig. 1 The relationship between potency (log $1/C_{obs}$) and the Hammett σ constant that describes the electronic effect of substituents. The data are from [7]

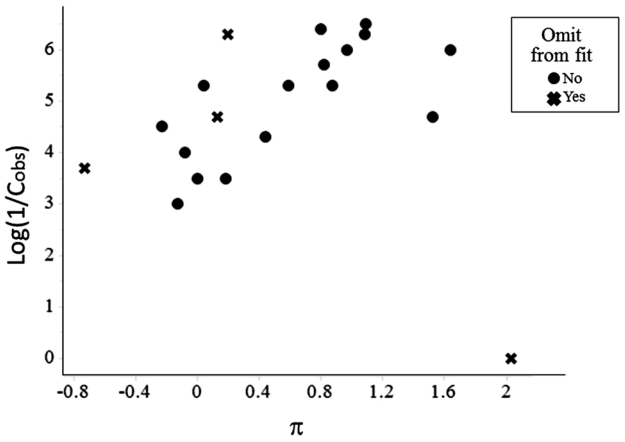

Fig. 2 The relationship between potency (log $1/C_{obs}$) and the Hansch-Fujita π constant that describes the hydrophobic effect of substituents. The data are from [7]

[54, 80]. They would consider electronic effects monitored by Hammett σ values, steric effects monitored by Taft E_s values, and 1-octanol–water log P using π to designate the difference in log P of the substituted molecule compared to the parent. Hansch suggested a parabolic term in log P to account for the optimum hydrophobicity such as that reported by Fieser and Veldstra. The Hansch-Fujita equation is expressed as follows:

$$\log(1/C) = \rho\sigma + a\pi + b\pi^2 + cE_s \tag{4}$$

in which σ is the Hammett constant for the electronic effect of the substituent and π is defined by the difference in log P of the substituted compound compared to the parent:

$$\pi_X = \log P_x - \log P_H \tag{5}$$

However, this formulation of a multi-parameter QSAR required fitting an equation in more than one variable, multiple regression analysis. Although least squares fit of a line between two properties, simple regression analysis, was common practice in many disciplines, it is claimed that the classic paper by Jaffé [45] introduced the method to physical organic chemists. He indicated that rather than drawing a line by eye, a least-squares method should be used. From that time on simple regression analysis was standard practice for evaluating structure–activity relationships. However, in the 1950s and early 1960s, to calculate one simple least-squares line took hours on a mechanical calculating machine. One such machine required a visit from a repairman if one happened to divide by zero—later models included a button to reset it. There was no printing capability, so each calculation had to be repeated, often several times, to ensure that no error was made. When considering two predictor variables, Taft and Kreevoy avoided the limitation of the calculator by keeping one

of the variables constant [81]. At best, it certainly would be tedious to calculate a multiple regression equation on such a device.

In a lucky break, Geology Professor Donald B. McIntyre, the leading proponent of computers at Pomona College, had already been using a Clary DE-60 when in 1960 he persuaded Frank R. Seaver, the Los Angeles industrialist whose financial backing created the Seaver Science Center at the college, to donate a Clary DE-60 to the chemistry department [82]. The DE-60 was a desk-size programmable electronic calculator. It had 18 bit words and 32 words of memory with up to 128 additional words. It was called an electronic computing calculator and was built into a desk [83]. A type bar typewriter and a 10-key adding machine were on the top of the desk. Inside the desk were the sealed circuit modules, a bank of PC boards, and the programming plug boards into which programs were wired. Not only was McIntyre responsible for acquiring the computer, but his enthusiasm for the technology led him to oversee the calculation of the multiple regression equation. In Professor Hansch's words "It was a complicated process in which three "boards" full of holes were wired to carry out three steps. One first entered the data using board one, then with the second board the data matrix was inverted, and with the third board the results were printed out. As chance would have it, MacIntyre's help in writing our first program was crucial, as I had had no thought of ever needing a computer. The limit of the Clary was to deal with three terms, which were all that we needed at this time" [12]. It should be noted that, in contrast to current practice, McIntyre was not a co-author on any QSAR publication. (McIntyre was prominent in his own sphere: he was an early adopter of the computer languages APL and J as well as a geologist recognized for his applications of computers to geology and investigations of early geological pioneers [84].) Even if all of the other keys to inventing QSAR had been present, it would not have been invented without the means to solve a multiple regression equation, in other words, it would not have been invented without access to a computer.

Equation 6 describes the fit of the data:

$$\log\left(\frac{1}{C}\right) = 3.37(\pm 0.18) + 2.28(\pm 0.34)\sigma + 4.10(\pm 0.47)\pi - 2.15(\pm 0.33)\pi^2 \quad (6)$$

The statistics of the fit are: $R^2 = 0.913$, $s = 0.37$, $n = 16$. Four compounds were omitted from the calculation. Note the significant role of Hammett σ as well as the terms in π. Figure 3 shows the relationship between the observed and calculated log (1/*C*).

Although the publication in 1962 was the first QSAR report, it was only a year later that the method was generalized. The second publication extended the correlation on plant growth regulators but also included an analysis of

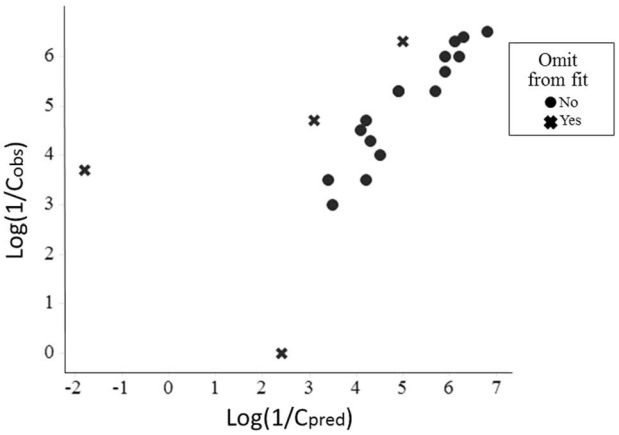

Fig. 3 The relationship between the observed potency (log $1/C_{obs}$) and that calculated from Eq. 6, (log $1/C_{pred}$). The data are from [7]

chloramphenicol analogues [35]. By 1964 they had enough experience to propose that this is a general method [85].

The publication of the first QSAR paper in 1962 was a landmark in medicinal chemistry in that it suggested to the community that is possible to forecast the biological potency of a compound before it is synthesized. Furthermore, the work was novel in that it considered that several features of substituents provide a quantitative and independent influence on biological potency; that the relative hydrophobicity of analogues could be described with a π value by analogy to Hammett σ constants for electronic effects; that the optimum π value could be approximated by a parabolic fit of potency with π; and that a computer could be used to generate the fit to the hypothetical equation.

Observation of the importance of log *P* in many datasets

Buoyed by their early success with the QSAR equation, in the 1964 they published a regression analysis of the antibacterial activity of penicillins [86]. The generality of the method was demonstrated by QSARs that showed the dependence on log *P* of the penetration of benzene boronic acids into brain and tumor, the relative potency of barbiturates, auxin activity, hypnotics, and antibacterials [87–91]. The capstone of this work was a review article, just seven years from the first QSAR, in which Hansch reports 43 equations that correlate biological activity with π or log *P* values [56]. He concludes: "The evidence in hand is that log *P* or π can enable us to employ computers in a numerical analysis

of biochemical structure–activity problems." By 1969 the group had published 34 additional articles in addition to the three seminal reports. Four of these were published in general journals. Of those in specialized journals, 13 were in journals related to medicinal chemistry, six related to pharmacology, seven related to biochemistry, one related to botany, two related to organic chemistry, and one related to polymers: Thus the method was applied to a range of topics of interest. Of the 30 specialized publications, only two showed no dependence of bioactivity on log *P*.

The work continued in the absence of Fujita who returned to Kyoto University to energetically pursue the application of QSAR to compounds of agricultural interest [92]. By 1972 Hansch and Dunn found a significant linear relationship between log *P* and biological activity in 123 datasets but no such relationship in ten [93]. This work was complemented the next year in a study by Hansch and Clayton of the parabolic relationship between log *P* and biological activity [94]. They report 167 datasets for which there is a significant parabolic correlation. Thus by the mid-1970s it was established that there is often a relationship between biological activity and log *P*. It can be appreciated that by 1982 the original publication of the method was recognized as a citation classic [12].

The 557-page book by Hansch and Leo summarize the results of QSAR investigations until 1995 [13]. They report the significant influence of log *P* on the structure–activity relationships in separate chapters on non-specific toxicity; proteins and enzymes; metabolism, both intermediary and of xenobiotics; mutagenesis, carcinogenesis, and anti-tumor efficacy; agents that act in the central nervous system; antimicrobials; and pesticides. However, not all datasets show a dependence on log *P* [95]. The search for QSARs continued unabated until 2011, the year of Hansch's death [96]. Google Scholar identified 88 articles published by Hansch after the 1995 book.

The Hansch group maintained a database of their equations. It now contains 8300 QSARs for biological entities [14]. As of today Google Scholar reports 2849 citations to the 1964 formulation by Hansch and Fujita. Thus, although Hansch did not expressly concentrate on hydrophobicity, the results of his work highlight its importance.

It is worth noting that QSAR has limitations [97]. Frequently, not all observations in a dataset fit the proposed equation. For example, note the results shown in Fig. 3. These outliers can sometimes be explained, but are troublesome non-the-less [98–102]. Researchers sometimes make errors in developing their QSAR [103]. Undoubtedly, there are datasets for which a QSAR cannot be found; some of these might have been investigated by the Pomona group but the results never published.

In 1997 Chris Lipinski published his highly-cited paper that stated that for optimum permeability a molecule should have a log *P* of less than 5, a molecular weight less than 500, fewer than five hydrogen bond donors and fewer than ten hydrogen-bond acceptors [104]. There is no question that this report stimulated the interest of scientists in many fields in log *P*—no longer would QSAR equations and computer-aided molecular design specialists need to be involved.

Sources of log *P* values

In order for QSAR to be used for many different sets of molecules it was necessary to have a means to provide the necessary log *P* or π values. Hansch and Fujita capitalized on other's observations of the apparent constancy of substituent effects on hydrophobicity. Accordingly, they measured the partition coefficients for 203 compounds, which allowed them to calculate π values for 67 substituents on eight different parent molecules [105]. The π value of a substituent is constant if it is not conjugated with the polar group on the parent molecule; if it is conjugated, then the difference in the π value compared to –H is dependent on Hammett σ. They proposed three sets of π values; π_n or normal π values, π^- values for substituents on phenols and anilines, and π^+ values for compounds with strong electron-attracting groups such as cyano or nitro that are conjugated with the parent substituent.

The Hansch group continued to measure partition coefficients and tabulate π values. Ultimately, hundreds of π-values were determined for both aromatic and aliphatic systems. A second 1995 book contains a table of π, σ, and *Es* values as well as an exhaustive tabulation of measured literature or Pomona log *P* values [106]. Hansch's long-time collaborator Al Leo maintains a master file of measured partition coefficients that now includes more than 60,000 values [14]. These π-values and measured log *P*'s provide other workers key information to use for their own QSAR work.

Leo also studied the structure–activity relationships of log *P* values [107] and, as did others [108], devised a method to calculate log *P* from chemical structure [109]. After continuous refinement by Leo, in 1983 Dave Weininger automated the calculations in the computer program CLOGP, which continues to be refined [110]. CLOGP remains a popular program to calculate log *P*, but there are also a number of other methods to do the same thing [111, 112]. Most of these, at least originally, require a computer specialist to perform the calculation. All these programs make use of the extensive database of measured values collected by the Pomona group.

The final step in making log *P* available to the medicinal chemist is to provide a desk-top tool to calculate log *P*. By the late 1990s the popular chemical structure drawing program, ChemDraw [113], provided the means to calculate log *P* from a drawn structure [111]. Around the same time,

web-based desktop programs also included the same capability [114–118].

1-Octanol as a reference solvent for hydrophobicity

Although Meyer and Overton used olive oil for their measurements of hydrophobicity, Hansch discarded this idea because the composition varies from lot to lot. Instead he chose to do the measurements in 1-octanol, which is available commercially in pure form. 1-octanol has the advantage over pure hydrocarbons in that drug-like compounds are soluble enough in it that one can actually measure a partition coefficient. Each gram of 1-octanol saturated with water contains 48.91 mg water, which translates to approximately one water molecule to every three molecules of 1-octanol [119]. In addition, because it contains a hydroxyl group, 1-octanol can form hydrogen bonds with solutes—the result is that an 1-octanol–water log *P* is a composite of hydrophobicity and hydrogen bonding. None-the-less, 1-octanol–water log *P* measurements have become the benchmark for studies of hydrophobicity.

Although theoretically hydrophobicity would be measured by partitioning between a hydrocarbon solvent and water, this is not possible for practical reasons, mainly because most compounds of interest partition very weakly into a hydrocarbon. In addition, if substances with polar functionality do partition to a hydrocarbon, they frequently carry along a water of solvation, which complicates interpreting the results in terms of pure physical chemistry.

Recalling that hydrophobicity depends on the properties of water and not that of the non-polar phase, it is not surprising that there is a correlation between the relative log *P* in 1-octanol and in other solvents. For various alcohols there is a 0.99 correlation with only the intercept changing. However, if the nonpolar phase does not contain a hydroxyl group, then the log *P*s of hydrogen bond donor and hydrogen bond acceptor solutes fall on different lines. In fact, one experimental measure of hydrogen bond strength can be derived from the difference between the 1-octanol–water log *P* and the cyclohexane–water log *P* [120]. In addition, the relationships between log *P*s of different solvents support the use of various HPLC methods to measure relative log *P* values.

Discussion

This report illustrates the various factors that come into play to precipitate a change in community thinking, in this case the invention of QSAR and its use to highlight the importance of hydrophobicity in the biological potency of small molecules. The first factor is the status quo—what "everyone" knows or thinks that they know. For organic chemists such as Corwin Hansch, this was the Hammett equation. After all, Jaffe's 318 references suggest that this is a powerful method to analyze structure–activity equations. Accordingly, Hansch spent more than a decade trying to fit the data on plant growth regulators into the Hammett equation. The second factor to precipitate a change in thinking is frustration that the current best methods don't provide a satisfactory answer. A third factor is to incorporate ideas from a different discipline, in the case of QSAR to consider oil–water partition coefficients as a means to interpret the structure–activity relationships. Equally frustrating is that abandoning the Hammett equation to concentrate on 1-octanol–water log *P* also does not explain the structure–activity relationships. The fourth factor on the way to produce something new is insight, this is, as suggested by Toshio Fujita, to consider several properties to explain the relationships. A fifth factor is luck: In this case that Toshio Fujita was selected as a postdoctoral fellow because, although he was selected because he had done some quantum chemical calculations, in addition he was well-versed in the literature of plant-growth regulators, the Hammett equation, and Taft's work. He also had done research that led to rebuttals of both competing theories of plant growth regulators structure–activity relationships. In another astounding piece of luck, not only did Pomona College have an early primitive computer when others were tied to calculators, but it also had an enthusiastic computer whiz, Donald McIntyre who was a faculty member in the geology department. These factors led to the development of QSAR.

However, just having QSAR did not lead to the recognition of the importance of log *P* in biological structure–activity relationships. It took Hansch's persistence to discover and publish thousands of QSARs and his observation that log *P* was either the sole property or a statistically important property in essentially all of these equations. It still wasn't enough to know that log *P* is important, because for scientists to use log *P* in their own research, they had to be able to calculate it easily and conveniently. This need was satisfied by the various programs to calculate log *P*, one of the first to be available was from the Pomona group.

In summary, it is a combination of knowledge of the literature, frustration with standard methods, borrowing ideas from a related field, inspiration, luck, and persistence that led to the recognition of log *P* as a key factor in biological structure–activity relationships. The particular synergism of Corwin Hansch and Toshio Fujita coupled with the computer savvy of Donald McIntyre led to a tool that forever changed the thinking of chemists pondering the biological activity of small molecules.

Epilogue When I learned about the periodic table as a high school student I became convinced that chemical knowledge could solve

problems in biology. This led me to select a combined chemistry-zoology major at Carleton College, which in turn led me to a two-year stint (1958–1960) as an assistant in the chemical pharmacology group at Abbott Laboratories. Dr. J. D. Taylor, leader of the group, emphasized that biological properties of molecules are the result of their physical properties, not their structure per se. When our team found the clinical candidate pargyline, Dr. Taylor arranged for the analytical department to measure the pK_a's and chloroform-water partition coefficients of the analogues. I left Abbott to enroll in graduate school at Northwestern University (1960–1964) as a physical biochemistry major in the chemistry department. While at Northwestern I was well indoctrinated in the role of hydrophobic interactions in protein structure but also in the traditional physical organic techniques such as the Hammett equation. Upon return to Abbott I became involved in pharmacokinetics, measuring drug levels as a function of time and fitting the results with non-linear regression. I also observed that the chemists who were searching for a better pro-drug for a compound of interest seemed to use any alcohol at hand with no thought other than its availability for synthesis. All of this was background for my 1967 meeting Corwin Hansch who was seated next to me at a formal dinner party at Pomona College. I was completely fascinated at his description of QSAR. We met the next day to generate a correlation between the rate of in vitro metabolism that I had measured on some common drugs and the octanol-water partition coefficients that his group had measured. This changed the course of my career.

I am puzzled as to why I, or in fact no one at Abbott, had known about Hansch's work. By the time that I met him his group had published at least a dozen papers in high-impact journals.

Martin YC, Hansch C (1971) The influence of hydrophobic character on the relative rate of oxidation of drugs by rat liver microsomes. J Med Chem 14:777–779.

Martin YC, Martin WB, Taylor J (1975) Regression analysis of the relationship between physical properties and the in vitro inhibition of monoamine oxidase by propynylamines. J Med Chem 18:883–888.

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