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Philip S. Magee: a life in QSAR

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Abstract A brief account of the career of Philip S. Magee, a distinguished member of the QSAR community.

Keywords QSAR · Phil Magee · Structure–activity relationships · QSAR prehistory

Introduction

The purpose of this symposium is to honor a talented and inspirational colleague who has been a major figure in QSAR for more than 30 years—Philip S. Magee. Phil was born in 1926. He graduated high school and then went into the navy at the age of 18, When the war ended he was mustered out and went to the University of Southern California, receiving his B. S. in Chemistry in 1952. He then enrolled in a doctoral program at the University of California in Los Angeles from which he graduated with a Ph. D. in physical organic chemistry 3 years later. Phil then was hired as a research chemist by the Chevron Ortho Division of Standard Oil, which specialized in agricultural chemicals. As a chemist working on pesticide development he was very successful, he not only produced a number of patents for phosphorus and sulfur based pesticides but had two of his inventions, acephate (Orthene 1971) and methamidophos, (Monitor 1973), manufactured. In the course of this work Phil became interested in the rational design of bioactive molecules.

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The dark ages of structure–bioactivity relationships

In order to understand the development of QSAR a brief historical background is required. We may begin by noting that the problem of correct empirical formulas was not solved until the famous International Congress of 1860 at which Canizzaro demonstrated that Avogadro's law of combining volumes could be used to derive the correct empirical formula for simple compounds. The concept of molecular structure was developed largely by Kekule, Couper and Crum-Brown between 1858 and 1870. Nevertheless, in spite of the lack of knowledge of composition and structure, Blake in 1841 [1] noted that "salts of isomorphous bases have a similar action (bioactivity)". This seems to be the first example of an attempt to relate the bioactivity of some compounds to a physical property. Horsford reported in 1851 [2] that the taste of some compounds could be related to their composition. Pelikan [3, 4] observed that toxic effects depended on composition. Borodin in 1858 [5] stated that "By comparing poisonous substances with each other one came to realize that their toxicological properties and chemical makeup are closely interrelated. The first thing noted was the fact that that many substances consisting of the same elements or taking part in similar chemical reactions also exert similar actions on the organism." In 1868 Crum-Brown and Fraser [6] proposed the existence of a mathematical relationship between structure and bioactivity. In 1877 Reynolds [7] published a paper entitled "The Influence of Chemical Constitution on Physiological Activity". All of the work described above is preliminary. It is now convenient to distinguish three levels of structure activity relationship:

1. A structure–activity relationship (SAR) results when a specific bioactivity occurs in a set of compounds that

have one or more functional groups and/or fragments in common. It may also result from homologous sets of the type $CH_3(CH_2)_nY$ [8] or from bioisosterism [9, 10].

2. A qualitative structure–activity relationship (qSAR) results when some specific bioactivity is shown to be dependent on some measurable molecular property though no equation relating the two quantities has been obtained. The work of Richardson [11] showing that narcosis depends on molecular weight (and therefore on the number of carbon atoms, n_C); and of Overton [12], Meyer [13] and Baum [14] showing that it depends on the olive oil/water partition coefficient, is in this category.
3. A quantitative structure–activity relationship (QSAR) is obtained when some specific bioactivity is mathematically related to one or more structural parameters. The earliest example of a QSAR seems to be due to Kamm [15] who proposed the Kamm–Traube equation:

$$Ba_n = BA_2 * W_n/W_2 * 3^m \quad (1)$$

where W_n and W_2 are the molecular weights of the nth and 2nd members respectively of a homologous data set, BA_n and BA_2 are the corresponding bioactivities, and $m = n - 2$. The first member of a homologous data set generally has a bioactivity that does not fit Eq. 1.

Many other examples of types of QSAR were reported between 1921 and 1966.

In 1937 L. P. Hammett [16] proposed the Hammett equation [17] as method for obtaining quantitative structure–reactivity relationships (QSRR) for reactions of 3- or 4-substituted benzene data sets with a reaction site in 1. The equation may be written as:

$$Q_X = \rho\sigma_X + h \quad (2)$$

where Q_X is the reactivity of the compound bearing the X substituent, σ_X represents the electrical effect of X, the slope ρ is a measure of the sensitivity of Q to electrical effects and the intercept h is the calculated value of Q when X is H.

The Taft–Pavelich equation: [18]

$$Q_X = \rho^*\sigma_X^* + \psi E_{S,X} + h \quad (3)$$

was proposed to account for electrical and steric effects when X is bonded to sp^3 hybridized C-atoms. Attempts to apply Eqs. 2 and 3 to bioactivity data were only partially successful. They did however supply the inspiration for the work of Hansch et al. [19] who between 1962 and 1966 proposed the equations:

$$pC_X = a_1\pi_X + a_2\pi_X^2 + \rho\sigma_X + a_o \quad (4)$$

where:

$$\pi \equiv \log P_X - \log P_H \quad (5)$$

and P is the octanol/water partition coefficient; while pC is −1 log (effective concentration) of the compound bearing the substituent X. In a few years the Hansch–Fujita model became the accepted paradigm for QSAR studies.

Further developments

In 1975 the first Gordon Conference on QSAR was organized. The attendees were medicinal and agricultural chemists interested in the design of bioactive molecules, statisticians, and physical organic chemists specializing in correlation analysis (linear free energy relationships). I was one of the latter. Phil attended this meeting and met others with similar interests. I became a close friend of Phil at the second QSAR Gordon conference in 1977. We spent a lot of time together discussing our recent results, proposing new ideas, and going over the latest literature. I visited his home and he visited mine.

In 1981 a number of us decided we needed a periodical devoted to QSAR and related topics, which led to the foundation of the QSAR journal, edited by Joe Seidel and then published by Verlag Chemie. Both research papers and abstracts of the literature were published. The editor of the abstract section was Ferenc Darvas.

After 28 years Phil retired from Chevron Ortho and founded his own consulting firm, Biosar Consulting. His company offered both statistical and molecular modeling and training programs in bioactive molecule design.

Phil also became an adjunct Professor at both Oregon State University and in the Department of Dermatology of the School of Medicine, University of California at San Francisco. Phil was the coeditor of three collective volumes, two of them in the ACS Symposium Series [20–22].

The founding of the QSAR society

In 1991 at the Gordon Conference Ferenc Darvas told me that the QSAR journal needed the support of a scientific society if it was to continue. After discussing the problem Phil, John Block, Jim King and I formed what is now the Cheminformatics and QSAR Society which now has 945 members. Phil became the first Chairman, Jim was Treasurer and John was secretary. The members of the society share a common interest in the relationship of molecular structure to biological activity.

Summation

Phil was active in developing QSAR involving dermatology in the last part of his life. He had a stroke in 2003, and battled back from its effects. After a short illness he died of cancer in 2005. He will be remembered as a good friend, a great colleague, and a significant contributor to the field.

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