Journal of Chromatography, 144 (1977) 285–286

CHROM. 10,503

Book Review

The hydrophobic fragmental constant; Its derivation and application; A means of characterizing membrane systems (Pharmacochemistry Library, Vol. 1), by R. F. Rekker, Elsevier, Amsterdam, Oxford, New York, 1977, XIX + 389 pp., price Dfl. 97.50, US$ 38.95, ISBN 0-444-41548-3.

Had it not been for the spectacular ascent of "reversed-phase" chromatography as the leading technique in high-performance liquid chromatography, this book could be of little interest to the readers of the journal. The magic of "hydrophobic" or "solvophobic" interactions, which are responsible for solute retention on non-polar stationary phases, however, is increasingly used by chromatographers to solve a wide range of separation problems very conveniently and efficiently. Therefore, the extensive literature in medical chemistry dealing with the hydrophobic properties of various biologically important compounds suddenly has become interesting for the potential of predicting retention behaviour in "reversed-phase" chromatography from "hydrophobicity" of solutes.

What the hydrophobic effect actually is still remains controversial as far as a rigorous thermodynamic treatment is concerned. Indisputably, it is a kind of non-covalent interaction which is literally caused by the hatred of water. This makes the thought of a hydrophobic bound *outré* with regard to orthodox textbook chemistry, whereas other non-covalent molecular interactions such as coulombic and hydrogen bonding, which are due to attraction between the species, have been long understood. Attraction and repulsion are easy to appreciate, they are ingrained in human nature. This may be the reason why scientists have had a relatively easy task in quantifying the corresponding forces on the molecular level and adequately describing the phenomena.

To deal with the world of biological molecules and to understand their interactions entirely we have to reach beyond the simplistic notions of love and hatred. The enlightment has come from the realization that not only governments and people but also molecules can act on the principle "the enemy of my enemy is my friend". Hydrophobic or more generally lyophobic interactions, which play an extremely important role in determining the architecture and dynamic behaviour of biological substances, arise from such a molecular attitude with the solvent, in particular water, playing the role of the enemy. As such "friendship" is not easy to understand, it is no wonder that the quantitative description of the phenomenon has been difficult and the progress is slow. Not having anything better to characterize the pertinent molecular properties, a relatively modest amount of partition coefficient data obtained in systems composed of water and a non-polar solvent have been subjected to a monumental statistical analysis in order to factor out some numbers on the hydrophobicity of the structural elements of the solute molecules.

Rekker's book is the latest comprehensive treatment of the subject which has been popularized by Hansch. It is an expansion of the author's work on hydrophobic fragmental constants which measure the hydrophobicity of structural elements in chemical compounds. Like the π-values introduced by Hansch and used widely, they are derived from partition coefficients obtained in suitable organic solvent–water systems. Although the subtitle promises a characterization of membrane systems, the accomplishments of the book in this regard are less noteworthy.

It is not easy to read the book for many reasons. At the beginning the uninitiated reader finds the *lingua franca* of this type of literature somewhat strange. The first terms encountered are SAR and QSAR, the acronyms for structure–activity relationship and quantitative SAR, respectively. The use of such terms is so widespread that in the preface feelings are expressed "in SAR-like terms". Nevertheless with some efforts the reader can acquire the skill to follow the text and it is a worthy undertaking.

The book presents a large amount of data distilled via correlation analysis but a cursory reading does not make it clear to a chromatographer how to use the material. To draw maximum benefits from the book, further reading of the pertinent literature may be required. It would have been desirable to have a more detailed general introduction to linear free energy relationships, the *point d'appui* of the whole approach.

What lies behind the vast data analysis and sometimes quodlibetic attention to minor details

is clear. Medicinal chemists and chromatographers both want to know how the chemical structure of a substance determines its behaviour in their respective systems. Some time ago, the center of such activities was in the realm of chromatography due to the need to identify the spots or peaks on the chromatogram. In the recent years, however, the main emphasis is shifted to predict the biological activity of a substance from its chemical structure. The reason for this is the high cost of biological testing of potential drugs as well as toxic or carcinogenic substances. In fact, by employing sophisticated statistical analysis with high speed computers, medicinal chemistry has made great advances in this regard while chromatographers have been preoccupied with the development of high-performance liquid chromatography.

Both chromatographic retention and biological activity can be described by linear free energy relationships which have been used by physical chemists to interpret the effect of structural parameters on chemical rates and equilibris. With biological compounds the so-called hydrophobic properties are of particular interest because an unambiguous definition of a hydrophobic free energy is difficult. Here, reversed-phase chromatography in its new form as practiced today can fill a gap.

For this reason anyone familiar with the accomplishments and potential of high-performance liquid chromatography would feel that the technique does not receive due attention in this book. This is probably owing to the fact that most data came from partition coefficients measured in octanol–water. Yet, the excellent treatise on the use and relevance of chromatographic measurements by Tomlinson in *Chromatographic Reviews*[1] should have been mentioned. This reviewer is convinced that modern liquid chromatography as a versatile, rapid microanalytical tool will play a significant role in collecting data for QSAR studies. The present gap can be eliminated when the QSAR people become acquainted with the potential and methodology of modern liquid chromatography and chromatographers supply enough evidence that their technique is superior to the classical methods.

With this in mind, Rekker's book can be not only a useful source of hydrophobic parameters to be used for quantitative structure–retention relationships, QSRR if you don't mind, but also a stimulant for the development of more refined chromatographic methods and means for collecting and analysis of data for use in QSAR.

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1 E. Tomlinson, *J. Chromatogr.*, 113 (1975) 1.

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