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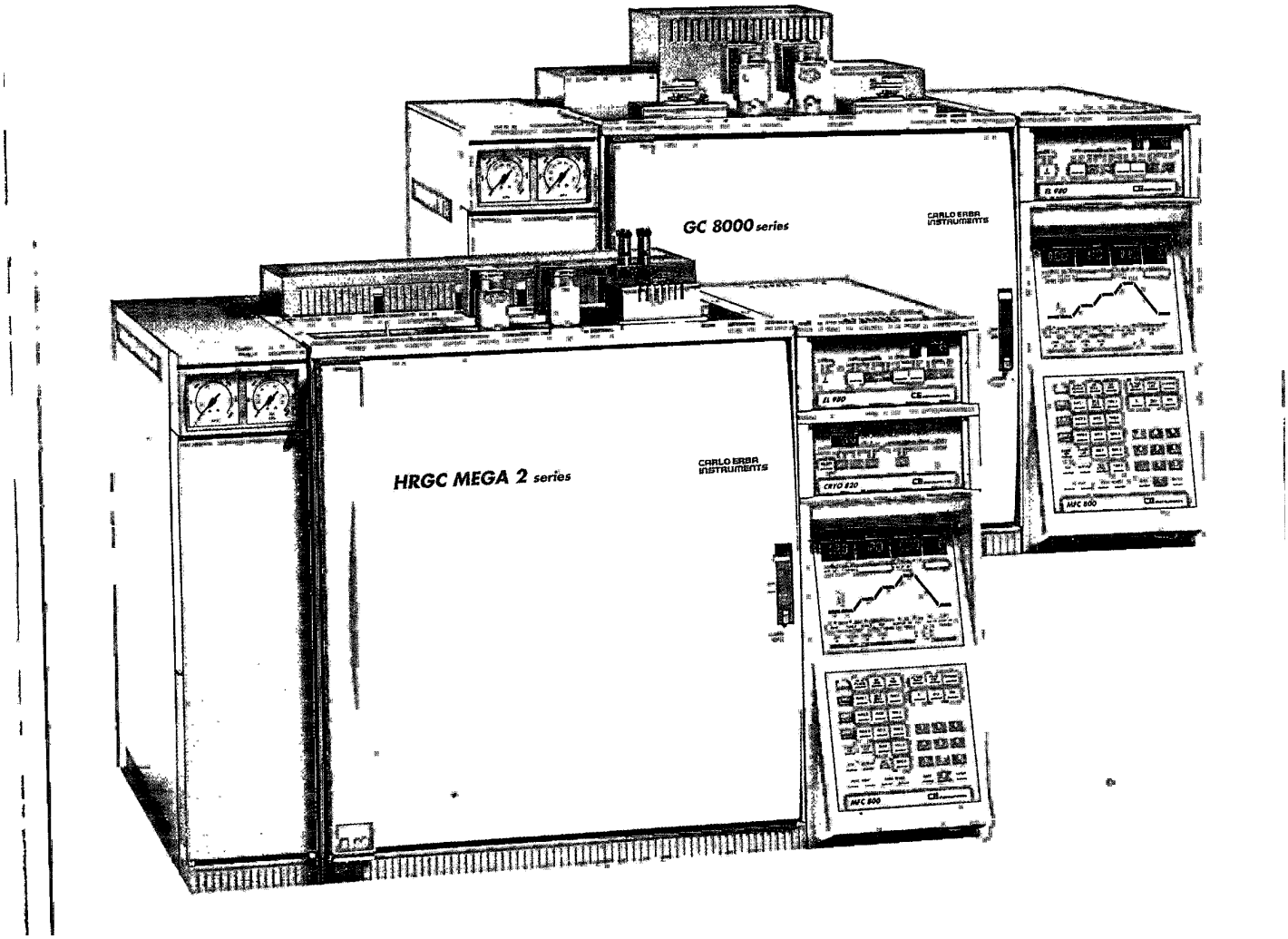

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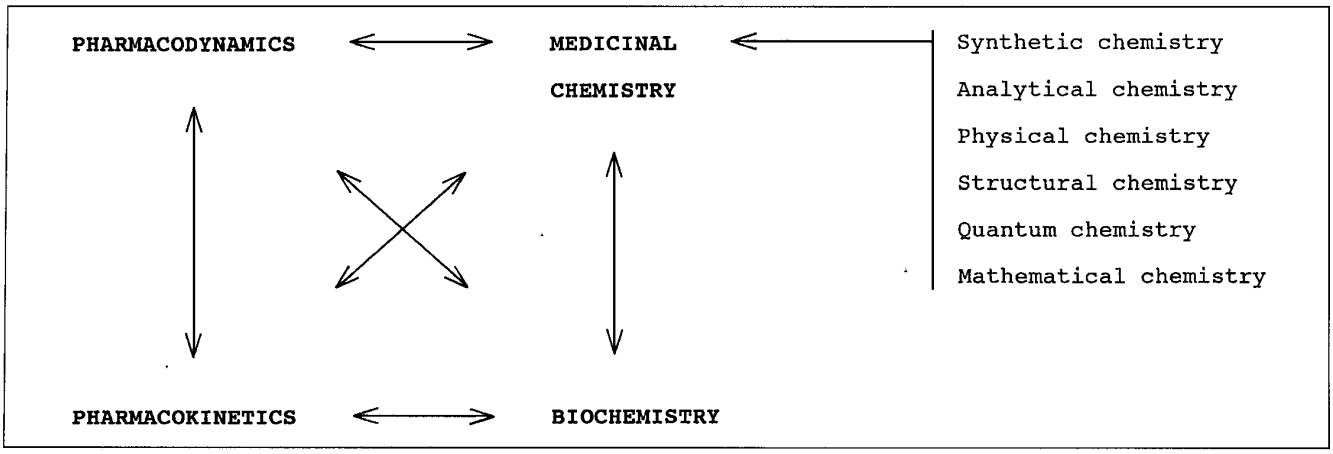

Figure. *The relation of medicinal chemistry with connected disciplines*

discoveries in the chemical sciences (*e.g.* synthetic chemistry), but the major contributions to progress should come from molecular biology and mathematics.

Molecular biology is having a major impact on molecular pharmacology and enzymology, and this in turn has begun to deeply affect the thinking and work of medicinal chemists. For example, the cloning of new receptor subtypes and of mutant receptors and enzymes obtained by site-directed mutagenesis has brought us closer to understanding the structure and functioning of these macromolecules. The impact on molecular-graphics studies and on lead generation and optimization is overwhelming.

It is not in the least fortuitous that the development of medicinal chemistry should parallel advances in *mathematical and computational sciences* and their applications. These theoretical advances, coupled to the fast technological evolution of computing machines, will continue to offer to pharmacochemists tools of ever increasing sophistication and efficiency.

In the longer run, however, the molecular level of conceptualization may reveal its limits. At this point, continued progress in medicinal chemistry may call for input from *systemic pharmacology*, in other words from a highly integrated and organismic pharmacology which may well be the clinical pharmacology of the future. In such a perspective, medicinal chemistry would become more 'therapeutic', thus providing a belated vindication of the French label 'chimie thérapeutique'.

The author is deeply indebted to Prof. *Lemont B. Kier*, currently holder of the Chair of Honour at the University of Lausanne, for many stimulating discussions and for his insightful correction of the text.

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[1] B. Testa, 'Drugs? Drug Research? Advances in Drug Research? Musings of a Medicinal Chemist', in 'Advances in Drug Research', Ed. B. Testa, Academic Press, London, 1984, Vol. 13, p. 1.
[2] B. Spilker, 'Missions, objectives, goals, strategies and tactics revisited', *Drug News Persp.* **1989**, *2*, 281.
[3] B. Testa, 'Pharmacokinetic and pharmacodynamic events: can they always be distinguished?', *Trends Pharmacol. Sci.* **1987**, *8*, 381.

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Hydrogen-Bonding Capacity and Brain Penetration

Han van de Waterbeemd* and **Manfred Kansy**

Abstract. Brain penetration has been reported to correlate with Δlog P, defined as log P (octan-1-ol/H_2O) – log P (alkane/H_2O). Another recent development, describing log P as the sum of a cavity or volume contribution and H-bonding capability, the latter expressed by $A_{solvent}$ values, prompted us to reinvestigate the properties accounting for brain penetration. It was found that A_{alkane} and the hydrophilic part of the *van der Waals* surface both correlate well with brain uptake. These findings offer new opportunities for the design of compounds which either should or should not be active at sites located

1. Brain Uptake and Physicochemical Properties

1.1. *The Δlog P Concept*

Numerous QSAR studies on CNS drugs have demonstrated that besides p*K*a and molecular size, lipophilicity is a highly significant contributor to brain penetration [1][2]. Partition coefficients measured in the octan-1-ol/H_2O system are mostly used as experimental assessment of the lipophilicity of a compound. However, it has been observed that neither octan-1-ol/H_2O (log P_{oct}) nor cyclohexane/H_2O (log P_{chex}) partition coefficients are predictive for brain penetration of H_2-

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receptor histamine antagonists [3][4]. From further investigation, a new concept emerged. It was found that a good correlation exists between the logarithm of the equilibrium brain/blood concentration ratios and the differences $\Delta\log P$ ($= \log P_{oct} - \log P_{chex}$) of partition coefficients in two different solvent systems. The *Ganellin-Young* group believed that $\Delta\log P$ accounts for H-bonding ability and reflects two distinct processes [3][4]. The $\log P_{chex}$ parameter could reflect partitioning into nonpolar regions of the brain, while $\log P_{oct}$ might account for protein binding in the peripheral blood. To target compounds into the brain by passive diffusion, therefore, one should minimize polar H-bonding groups and molecular size.

This $\Delta\log P$ concept has also been explored for skin penetration [5]. Skin penetration can be rationalized by considering inter- and intracellular routes. *Testa* and coworkers demonstrated that $\Delta\log P$ contains information on the capacity of a solute to donate H-bonds. In their view, the rate-limiting step in brain penetration is the donation of H-bonds of a solute to the hydrophilic parts of lipids in the blood-brain barrier [5][6].

1.2. *H-Bonding*

H-Bonding capacity has been extensively studied in solvatochromic equations for identifying the physicochemical properties governing solubility and partitioning phenomena [6][7]. Compilations of H-bond donor acidity (α) and acceptor basicity (β) can be found in the literature. However, these solvatochromic parameters can only be obtained with great experimental difficulty. Very recently, a new approach has been presented to assess α and β from log P data.

By various lines of evidence it can be shown that log P is a composite parameter, consisting of a cavity and a polarity term:

$$\log P = aV + \Lambda \qquad (1)$$

where V is the *van der Waals* volume and Λ accounts for polarity of the molecule including H-bonding capacity, and, therefore, $\Lambda = 0$ for alkanes. Λ for polar compounds is calculated from the difference in log P between the experimental value and the one calculated from the molar volume using the reference equation for the alkanes (*e.g. Eqns. 2* and *3*).

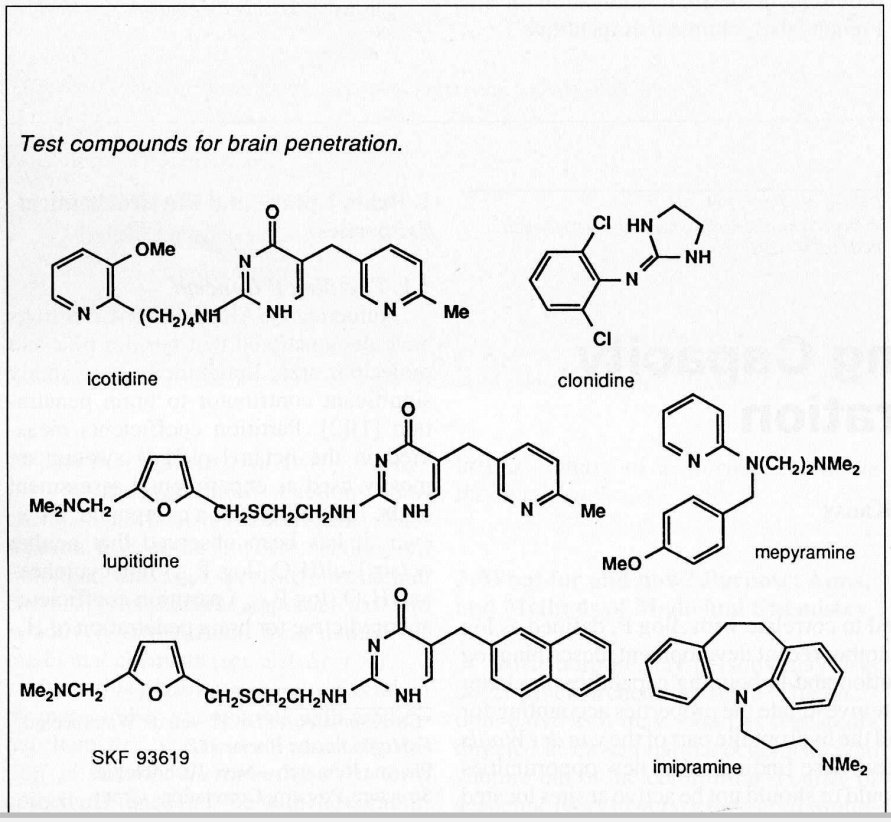
It was observed that Λ calculated from $\log P_{oct}$ values (Λ_{oct}) correlate quite well with H-bond acceptor basicity (β), while Λ calculated from log P values measured in alkane/H_2O systems $\log P_{alk}$ (Λ_{alk}) correlate with total H-bond capacity (α and β). Thus, experimental log P values and calculated molar volumes give elegant access to H-bonding capacities [8].

Table 1. *Physicochemical Properties of Alkanes*

Compound	V_M [a])	V_W [b])	V^0_{aq} [c])
Methane	30.3	17.1	37.3
Ethane	47.5	27.3	51.2
Propane	65.0	37.6	67.0
Butane	82.6	47.8	
Pentane	99.5	56.3	
Hexane	116.7	65.8	
Heptane	133.8	75.5	
Octane	150.6	85.2	

[a]) Molar volume calculated with our in-house program MOLOC. [b]) Molar volume taken from [8]. [c]) Experimental partial molar volume [8].

Test compounds for brain penetration.



1.3. *log P Measurement and Calculation*

The measurement of $\Delta\log P$ values is quite time-consuming, even with modern approaches such as centrifugal partition chromatography [9]. For certain series of compounds, it might even be excluded, since the log P of the compounds lies beyond the limits of reliable log P measurement. In such cases, calculated log P values might be of help, but of course only when such calculations are highly reliable. $\log P_{oct}$ can be calculated using the *Rekker* or *Leo-Hansch* fragmental approach [10]. *Rekker* and *Mannhold* recently have extended this approach and suggest an additive scheme for calculations of log P in alkane/H_2O [11]. A very crude estimate of $\Delta\log P$ values, therefore, can now be made, but great care is warranted.

As we have seen above, H-bonding properties are believed to play an important role in brain penetration processes. Taking advantage of these new Λ parameters, we have reinvestigated the brain

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