Journal of Computer-Aided Molecular Design, **15:** 337–354, 2001.
KLUWER/ESCOM

Substructure and whole molecule approaches for calculating log *P*

Raimund Mannhold[a,*] & Han van de Waterbeemd[b]
[a]*Molecular Drug Research Group, Building 22.03 Heinrich-Heine-Universität, Universitätsstraße 1, 40225 Düsseldorf, Germany;* [b]*Pfizer Central Research, Department of Drug Metabolism, Sandwich, Kent CT13 9NJ, UK*

Received 5 October 2000; accepted 23 October 2000

Key words: atom contribution methods for log *P* calculation, fragmental methods for log *P* calculation, lipophilicity, log *P*, log *P* calculation procedures, log *P* substructure approaches, predictive power of log *P* estimates, whole molecule approaches for log *P* calculation

Summary

Lipophilicity is a major determinant of pharmacokinetic and pharmacodynamic properties of drug molecules. Correspondingly, there is great interest in medicinal chemistry in developing methods of deriving the quantitative descriptor of lipophilicity, the partition coefficient *P*, from molecular structure. Roughly, methods for calculating log *P* can be divided into two major classes:

• *Substructure approaches* have in common that molecules are cut into atoms (*atom contribution methods*) or groups (*fragmental methods*); summing the single-atom or fragmental contributions (supplemented by applying correction rules in the latter case) results in the final log *P*.

• *Whole molecule approaches* inspect the entire molecule; they use for instance *molecular lipophilicity potentials (MLP), topological indices* or *molecular properties* to quantify log *P*.

In this review, representative members of substructure and whole molecule approaches for calculating log *P* are described; their advantages and shortcomings are discussed. Finally, the predictive power of some calculation methods is compared and a scheme for classifying calculation methods is proposed.

Introduction

Lipophilicity is a major determinant of several aspects of the disposition and biological action of drugs [1–3] and its use in new approaches like database searching additionally proves the impact of this physicochemical property. Experimental data for its quantitative descriptor, the partition coefficient *P* or its logarithm log *P*, exist for about 30 000 organic structures; this is negligible compared to the exponentially increasing number of compounds for which log *P* data are highly desired. Correspondingly, there is continual interest in medicinal chemistry in developing methods of deriving log *P* from molecular structure. The first method of calculating log *P* was the π-system, developed by Hansch and Fujita [4]. Shortcomings in the π-system led Rekker to develop the first fragmental contribution approach [5–8]. Since the definition of a fragment is not unambiguous, Broto et al. [9] and later on others developed calculation systems based on atomic contributions. All these methods have in common that molecules are cut into groups or atoms; summing the fragmental or single-atom contributions results in the final log *P*. In contrast, more recent approaches inspect the molecule as a whole; they use for instance molecular lipophilicity potentials, topological indices or molecular properties to quantify log *P* and some reflect the impact of 3D structure.

Up to date most calculation methods have been focused on log *P*, considering the molecule in its neutral state. Only very recently, attempts have been made to estimate log *D*, taking the ionization of molecules into account. Aspects of log *D* are out of the scope of this review which is intended to describe

*To whom correspondence should be addressed: E-mail: Raimund.Mannhold@uni-duesseldorf.de

representative members of substructure and whole molecule approaches for calculating log *P*; advantages and shortcomings are discussed. Finally, the predictive power of some log *P* models is compared and a scheme for classifying calculation methods is proposed.

Components of log *P*

Log *P* can be factored into various descriptors: major components are a size-related term and a contribution related to polarity or hydrogen bonding capability of a solute [10–12]. Testa and Seiler [13] described the steric (V_i) and lipophobic (Λ_i)components of the hydrophobic fragmental constant f_i:

$$f_i = 0.0534V_i + \Lambda_i \quad (1)$$

In later work [3] it was shown that this approach also applies to whole molecules:

$$\log P = 0.0309V - \Lambda + 0.346 \quad (2)$$

Another way of expressing this factorization of log *P* in qualitative terms [11] is that lipophilicity equals hydrophobicity minus polarity. Buchwald and Bodor have recently extended the Testa and Seiler approach [12]. They quantified polar group contributions and obtained the following equation (n = 320):

$$\log P = 0.032(\pm 0.0002)V_e - 0.723(\pm 0.007)N + \\ +0.010(\pm 0.0007)V_e I_{alk} \quad (3)$$

where V_e = molar volume; N = integer for polar groups to connect log *P* and molecular size, and I_{alk} = indicator for alkanes. N appears to correlate well with the solvatochromic hydrogen bond acceptor basicity β. Raevsky et al. [14] developed free energy-related H-bond donor and acceptor factors (ΣC_d and ΣC_a) and investigated their relationship to log *P*. Most important contributions come from the H-bond acceptor factors. Raevsky et al. [15] obtained the following equation (n = 2850; r = 0.970; s = 0.23), where α is the molecular polarizability:

$$\log P = 0.266(\pm 0.030)\alpha - 1.00(\pm 0.10)\Sigma C_a \quad (4)$$

The LSER methodology developed by Taft, Kamlet, Abraham and others has provided another framework to go a step further in describing polarity and hydrogen bonding contributions [16–22]. A general expression [17] for the calculation of log *P* values is:

$$\log P = vVx + rR_2 + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + s\pi_2^H + c \quad (5)$$

where Vx = McGowan's volume, R_2 = excess molar refraction, $\Sigma\alpha_2^H$ = solute overall hydrogen-bond donor acidity, $\Sigma\beta_2^H$ = solute overall hydrogen-bond acceptor basicity, π_2^H = solute dipolarity/polarizability. The most difficult and most criticised part of this approach is the determination of these so-called solvatochromic descriptors [22]. Furthermore, by using several size descriptors and several polarity/H-bonding descriptors in a single equation, there is a risk of parameter interrelation [22]. Relationships between the solvatochromic α, β and π^* values with Λ have been shown [23].

Substructure approaches

Substructure approaches (Table 1) cut molecules into fragments (fragmental methods) or down to the single-atom level (atom contribution methods). Molecules, however, are never mere collections of fragments or atoms. Thus, fragmental methods apply correction rules coupled with molecular connectivity. Most atom contribution methods work without correction factors. Exceptions exist and underline the similarity of substructure approaches:

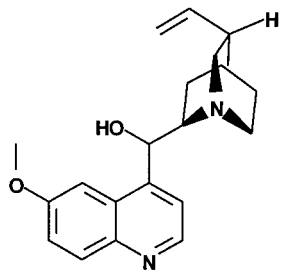
Fragmental methods	$\log P = \sum_{i=1}^{n} a_i \bullet f_i + \sum_{j=1}^{m} b_j \bullet F_j$
	f = fragmental constant
	a = number of fragments
	F = correction factor
	b_j = frequency of F_j
Atom contribution methods	$\log P = \Sigma\, n_i \bullet a_i$
	n_i = number of atoms of type i
	a_i = contribution of an atom of type i.

Fragmentation of a molecule can be somewhat arbitrary and any fragmentation approach has advantages and disadvantages. Fragments larger than a single atom can be defined, so that significant electronic interactions are comprised within one fragment, which represents a main advantage of using fragments. The advantage of atom contribution methods is that ambiguities are avoided; a disadvantage is that a huge number of atom types is needed to describe a reasonable set of molecules. Another shortcoming is the failure to deal with long-range interactions such as

Scheme 1. log *P* calculation for quinidine with a fragmental versus an atom contribution method.

fragmental method (Rekker / Mannhold)

Quinidine



fragments:	1 quinolinyl (- 1H)		+ 1.617
	1 O (aromatic)		- 0.450
	1 OH (aliphatic)		- 1.448
	1 N (aliphatic)		- 2.074
		sum	**- 2.355**
CH residual:	$C_{11}H_{18}$		+ 4.893
		sum	**2.538**
corrections:	proximity effect (+ $2C_M$)		+ 0.438
	electronegativity facing bulk (- $2C_M$)		- 0.438
	O-C-Ar (+ $1C_M$)		+ 0.219
log *P* exp 3.44		**log *P***	**2.757**

Calculation starts with the gross formula $C_{20}H_{24}N_2O_2$; definition of fragments leaves the CH residual; calculation is finalized by application of correction rules.

atom contribution method (Ghose / Crippen)

type	description	frequency	contribution
2	C in CH_2R_2	2	-0.9748
3	C in CHR_3	2	-0.7266
5	C in CH_3X	1	-1.0824
6	C in CH_2RX	2	-1.6740
8	C in CHR_2X	2	-1.0420
15	C in $=CH_2$	1	-0.1053
16	C in =CHR	1	-0.0681
24	C in R - - CH - - R	4	+0.0272
25	C in R - - CR - - R	2	+0.3200
26	C in R - - CX - - R	2	-0.2066
27	C in R - - CH - - X	1	+0.0598
46	H attached to C^0_{sp3} with no X to next C	1	+0.4410
47	H attached to C^1_{sp3} or C^0_{sp2}	16	+5.3488
48	H attached to C^2_{sp3}, C^1_{sp2} or C^0_{sp}	1	+0.3161
50	H attached to heteroatom	1	-0.3260
52	H attached to C^0_{sp3} with one X to next C	5	+1.8475
56	O in alcohol	1	+0.1402
60	O in Al - Al, Ar_2O, R • • O • • R or R-O-C=X	1	+0.2712
68	N in Al_3N	1	+0.3954
75	N in R - - N - - R or R - - N - - X	1	-0.1106
		log *P*	**2.852**

R: group connected to C; **X:** heteroatom; **=:** double bond; **- - :** aromatic bond; **• • :** aromatic single bond (e.g. C-N in pyrrole); **subscripts** give the hybridization state and **superscripts** the formal oxidization number.

Table 1. Substructure approaches.

Program	Fragmentation	Correction	Reference
	Fragmental		
CLOGP	200 fragment values*	25 correction rules*	[27–31]
Σf, manual	126 fragment values	10 correction rules	[5–8]
PROLOGP_cdr	126 fragment values	10 correction rules	[36]
Σ *f-SYBYL*	169 fragment values	13 correction rules	[34, 35]
SANALOGP_ER	302 fragment values	13 correction rules	[37]
KLOGP	68 contribution values	30 correction factors	[38]
LOGKOW	144 group contributions	235 correction factors	[39]
ACD/Log P	537 group contributions	2206 correction factors	[40, 41]
CHEMICALC	9 basic atomic, 415 basic group and 70 extended group contributions	–	[42]
HLOGP	1994 holograms		[43]
	Atom contribution		
MOLCAD, TSAR, PROLOGP_atom	120 atom contributions	–	[44–47]
ALOGP98	68 atom contributions	–	[48, 49]
SMILOGP	atom contributions	–	[50]
XLOGP 2.0	90 atom contributions	10 correction rules	[52]

Substructure approaches have in common that molecules are cut into atoms or groups; summing the single-atom or fragmental contributions (plus application of correction rules in the latter case) results in the final log P. Fragmental methods usually apply corrections; CHEMICALC represents the only exception. Atom contribution methods normally work without correction factors with the exception of XLOGP. Programs given in italic and bold are commercially available; remaining programs are available from the authors (see also Table 4). * = according to ref. [28], present data not known.

found e.g. in *p*-nitrophenol. Substructure approaches fail to calculate structural isomers and do not consider conformational flexibility. Atom contribution [24] and fragmental methods [25, 26] have been extended to cope with these shortcomings.

Calculation of log P via a fragmental method and an atom contribution method is compared in scheme 1 for the classical compound quinidine, to demonstrate the principal differences between fragmental (application of correction rules) and atom contribution methods (huge number of atom types).

Substructure approaches: fragmental methods

CLOGP – Hansch and Leo [27–31] developed a fragmental system, which is based on the principles of '*constructionism*'. The basic fragmental values were derived from accurately measured log P data of a small set of simple molecules such as hydrogen and methane, then the remaining fragment set was constructed. Considerable effort went into the definition of fragmentation rules as represented by the introduction of the concept of isolating carbon (sp^3 carbon with at least two bonds linked to other carbon atoms). In contrast to the Σf-system (see below) a correction for branching is applied. In [28] 200 fragment values and 25 correction factors were given. The method was first adapted for computational use by Chou and Jurs [32]. Since long it is marketed as CLOGP, the most frequently used log P calculation program. From version 4.0 on CLOGP includes as an important improvement of its performance the socalled FRAGCALC algorithm [33], which was devised to calculate fragment values from scratch. It is based on a test set of 600 dependably measured fragments having only aliphatic or aromatic bonds. Thus, newer versions of CLOGP bypass its former drawback, i.e. exhibiting up to 20% missing calculations in complex, large databases.

Σf*-system* – The first fragmental method was developed by the Rekker group [5–8]. Experimental log P's of simple organics were used to derive fragmental values by Free–Wilson type regression analyses; hence this approach has been labeled '*reductionistic*'. The development of the Σf-system comprised three main phases. The first period resulted in a valuable system

for log P calculation based on 126 fragment values. Fragmentation leaves functional groups with direct resonance interaction intact. Fragments range from atoms over substituents to complicated, in particular heterocyclic ring structures; fragments are differentiated according to aliphatic or aromatic attachment. Regression analyses revealed systematic differences between measured log P and log P calculations based on the mere summation of fragment values. These differences could be attributed to chemical characteristics of the molecules, which in turn allowed the definition of correction rules. A closer inspection of the correction values revealed that they represent multiples of a constant value of 0.289, known as the 'magic constant' (C_M). This approach is known as the *original* Σf*-system* [5–8]. In the second phase some intriguing points initiated a thorough revision of the original system, which resulted in a better fit of log P_{oct} for simple halo-alkanes and aliphatic hydrocarbons with Σf -data and a refinement of the correction factor C_M to a value of 0.219. Details of the *revised* Σf*-system* are given by Rekker and Mannhold [34]. A third phase was dedicated to the complex pattern of multi-halogenation in aliphatic hydrocarbons; for details see [35]. This paper gives the most recent version of the Σf-system with a listing of 13 correction rules and a tabulation of the f-values for 169 fragments, including 14 new heterocyclic fragments as well as doubly and triply halogenated methyls. The Σf-method is the only fragment method that allows manual log P calculation. For the application to large databases, however, computerized versions are available (Table 1). The original Σf-system is underlying PRO-LOGP_cdr [36]; Σf-SYBYL [34, 35] is based on the revised Σf-system and SANALOGP_ER [37] refers to an extended, revised Σf-system, which comprises an increased number of 302 fragmental constants.

KLOGP – Log P calculations based on an 'extended group contribution' approach were developed by Klopman et al. [38]:

$$\log P = b_0 + \Sigma b_i \bullet N_i + \Sigma F_j \bullet N_j \qquad (6)$$

N_i is the occurrence of the i th atom-centred fragment and N_j are the occurrences of particular fragments accounting for the interaction between groups whose influence on final log P is described by calculated correction factors F_j. KLOGP was derived via regression analysis ($r^2 = 0.93$; $s = 0.38$) from a database containing 1663 diverse organics. The basic atom-centred groups and the correction factors were automatically identified by the artificial intelligence system CASE (Computer Automated Structure Evaluation). A total of 98 contribution values and correction factors are given; corrections in particular reflect tautomerization effects, zwitterion effects, proximity effects and conjugated multiheteroatomic effects.

LOGKOW – The 'atom/fragment contribution method', introduced by Meylan and Howard [37], is available as the KOWWIN software. Like the Σf-system it is a reductionist approach derived by regression analysis; the model is defined as:

$$\log P = 0.229 + \Sigma f_k N_k + \Sigma F_j N_j \qquad (7)$$

N_k is the occurrence of the k th fragment or atom type and N_j is the occurrence of the j th correction factor. The hydrophobic constants were evaluated by a first regression analysis of 1120 compounds without considering correction factors. The latter were then derived via linear regression of additional 1231 compounds correlating the differences between experimental log P and the log P estimated by the first regression model. The software is continuously upgraded; 144 atom/fragment values and 235 correction factors are listed in the version 1.54.

ACD/Log P – A last and quite promising example for pure fragmental methods is the ACD/LogP approach [40, 41]. Fragmentation rules are based on a definition of the isolating carbon (IC) that is not doubly or triply bonded to a heteroatom; it differs in several respects from the definition in CLOGP. Hydrogens, for instance, are never detached from IC's, eliminating the need for several structural correction factors. The ACD/LogP algorithm uses 532 group contributions, f, and 2206 intramolecular correction factors, F_{ij}. The following three-step procedure is underlying ACD/LogP calculations: a) structure fragmentation and assignment of f constants; missing fragments are estimated by atomic increments similar e.g. to Ghose/Crippen; b) assignment of implemented F_{ij} constants; missing interfragmental interactions are calculated by a polylinear expression similar to the Hammett-Palm equation and c) summation of the implemented and estimated f- and F_{ij}-constants. The training set included 3601 structures; fitting of experimental and calculated log P yielded an correlation coefficient of 0.992 and a standard deviation of 0.21. The main weakness of the approach is its use of large numbers of increments for aromatic interactions. A re-

markable advantage of ACD/LogP is that it correctly addresses tautomeric forms.

CHEMICALC – Suzuki and Kudo [42] published in 1990 a group-contribution model for calculating log P:

$$\log P = b_0 + \Sigma f_k \bullet \mathrm{N}_k \quad (8)$$

N_k is the occurrence of the k th fragment in the molecule. A training set of 1465 compounds was used to derive 9 basic atomic contributions, 415 basic group contributions, and 70 extended group contributions by multivariate regresssion analysis; no correction terms are applied. The preferential use of group contributions classifies the Suzuki/Kudo approach as a fragmental method, while the lack of correction terms is characteristic of atom contribution methods. This program is a component of the software CHEMICALC (Combined Handling of Estimation Methods Intended for Completely Automated Log P Calculation).

HLOGP – Viswanadhan et al. [43] recently described the development of a new log P model based on a novel double hologram approach. It was used to simultaneously consider longer and shorter fragments as well as minimizing 'fragment collisions', which refers to different fragment types occupying the same bin when the hologram length is smaller than the number of disctinct fragments. In the HLOGP approach, fragments of the size of 1 to 3 atoms were used for generating one hologram of length 997 for 931 molecules, with hydrogens considered explicitly. A second hologram of the same length was also associated with each molecule for fragments of the size of 4 to 7 atoms, with hydrogens considered implicitly. Then PLS regression with the entire 1994 hologram variables was used to develop a log P model, fine-tuning the relative contributions of longer and shorter fragments and incorporating intramolecular interactions into the model. HLOGP was developed using the Pomona starlist database; 90% of the database was used as training set and the remaining 10% as test set.

Substructure approaches: atom contribution methods

Ghose/Crippen approach – The group of Crippen [44–47] has described the development of a purely atom-based procedure, which exclusively applies atom contributions and avoids correction factors:

$$\log P = \Sigma \mathrm{a}_k \mathrm{N}_k \quad (9)$$

N_k is the occurrence if the k th atom type. Carbon, hydrogen, oxygen, nitrogen, sulfur, and halogens are classified into 110 atom types; after several revisions, the number of atom classifications has increased to 120 [44] obtained from a training set of 893 structures ($r^2 = 0.856$, $s = 0.496$). Hydrogen and halogens are classified by the hybridization and oxidation state of the carbon they are bonded to; carbon atoms are classified by their hybridization state and the chemical nature of their neighboring atoms. The complexity of the classification procedure is attested by a total of 44 carbon types alone. The Ghose/Crippen approach is currently the most widely used atom contribution method. Software packages in which Ghose/Crippen-based log P calculation is available are PROLOGP, MOLCAD and TSAR (see Table 1). ALOGP98 [48, 49] is a recent refinement of the original Ghose/Crippen approach aimed at considering earlier criticisms, in particular the chemical sense of atomic contributions. The new version comprises 68 atomic definitions obtained via SMARTS from DAYLIGHT. The chemical interpretation of the atomic definitions is improved by constraining several carbon atom types to have positive contributions to log P in the fitting process. The training set was expanded to the 9000 structures in the POMONA database, a standard deviation of 0.67 is reported.

SMILOGP – Convard et al. [50] presented a program that is based on the hydrophobic constants of Broto, Moreau and Vandycke [9] and that generates an extended connectivity matrix from the SMILES code of a given molecule. The extended connectivity matrix comprises six columns: first one contains the label of the atoms, the second the chemical type of atom, and the last four contain the bond type as well as the number of atoms connected with the atom under consideration. The connectivity matrix allows the determination of the atomic code for an atomic fragment $\mathrm{f_i}$ and then the attribution of its contribution to lipophilicity. Finally, the log P value is computed by summing the f_i values.

XLOGP – A further atom-additive method was published by Wang et al. [51]. In contrast to pure atom-based methods correction rules are defined. Atoms are classified by their hybridization states and their neighboring atoms. 76 basic atom types and 4 pseudoatom types for functional groups (cyano, isothiocyano, nitroso, and nitro) give a total of 80 descriptors in atom classification. To account for intramolecular in-

teractions, which affect hydrophobicity, the following correction factors were included in the model: (1) the number of 'hydrophobic carbons' (= sp^3 and sp^2 carbon without any attached heteroatom); (2) an indicator variable of amino acids; (3) presence of intramolecular hydrogen bonds, and (4) two corrections for 'polyhalogenation' (two or more halogens are attached to the same atom); the latter corrections differ depending on the presence or absence of fluorine. The program, written in the C language, is available from the authors.

Quite recently, the new version XLOGP 2.0 has been described [52]. The number of atom types to classify carbon, nitrogen, oxygen, sulfur, phosphorus and halogen atoms is increased to 90. Ten correction factors are derived to correctly handle hydrophobic carbon, internal H-bond, halogen 1–3 pair, aromatic nitrogen 1–4 pair, ortho sp^3 oxygen pair, para donor pair, sp^2 oxygen 1–5 pair, α-amino acid, salicylic acid and p-amino sulfonic acid. The training set to derive XLOGP 2.0 comprised 1853 compounds. The correlation coefficient for fitting this set to experimental log P is 0.93 and the standard deviation 0.349.

The preferential use of atomic contributions classifies XLOGP as an atom-based approach, but the use of correction factors is characteristic of fragmental methods. The use of correction factors might underly the excellent performance of XLOGP versus pure atom contribution methods.

Whole molecule approaches

Whole molecule approaches (Table 2) utilize descriptions of the entire molecule to calculate log P. These models attempt to circumvent shortcomings of fragmental approaches such as the simplification of steric effects, the failure to calculate log P for structures with missing fragments or the lacking differentiation between structural isomers. Whole molecule approaches use a) *molecular lipophilicity potentials (MLP)*, b) *topological indices* or c) *molecular properties* such as charge densities, surface area, volume and electrostatic potential to quantify log P.

Whole molecule approaches: molecular lipophilicity potential (MLP) and related methods

The MLP defines the influence of all lipophilic fragmental contributions of a molecule on its environment and offers a quantitative three-dimensional description of lipophilicity. At a given point in space, the MLP value represents the results of the intermolecular interactions between all fragments and the solvent system at that point. Two components are necessary to calculate the MLP: a substructure system and a distance function. The group of Dubost [53] was the first to introduce the MLP approach, using the Σf-system as fragmental method and a hyperbolic distance function. Fauchère et al. [54] applied the fragmental systems of Rekker and/or Hansch and Leo and an exponential distance function. Others use the atom contribution method of Ghose /Crippen and a hyperbolic distance function [55].

CLIP – The group of Testa [56] developed an MLP approach which is based on the atom contribution method of Broto et al. [9] and a modification of the distance function used by Fauchère et al. [54]. This MLP-based log P calculation procedure is available in the software package CLIP (Computed Lipophilicity Properties). The program allows the calculation of virtual log P values for individual conformers.

HINT – The program HINT [57–61] is another approach to reflect three-dimensionality by combining substructure contributions and conformational effects. The key parameter is the hydrophobic atom constant a_i, derived from Leo's fragment constants. HINT calculates hydrophobic atom constants using the following criteria: (1) the sum of atom constants within a fragment equals the fragment constant value, (2) bond, branching or vicinal halogen factors are applied to all eligible atoms, while polar proximity factors are applied to the central atom of fragments, and (3) superficial atoms are considered to be more important than central atoms.

MOLFESD – The group of Brickmann presented a new method for display and analysis of lipophilic/hydrophilic properties on molecular surfaces [62]. Their approach is based on the Ghose/Crippen concept as well as the concept of molecular lipophilicity potentials. It was demonstrated that a Fermi type distance function in molecular lipophilicity potentials can be used to map weighted increment values for Ghose/Crippen log P data onto the molecular surfaces. In an extension of this work [63, 64] it was shown that the transfer free energy for bringing a molecule from one solvent to another can be represented as a surface integral over the molecular contact surface with the solvent and accordingly a 'free

Table 2. Whole molecule approaches.

Program	Descriptors	Validation	Reference
	MLP and related approaches		
CLIP	molecular lipophilicity potential	MLR	[56]
HINT	hydrophobic atom constant, central and frontier atoms	MLR	[57–61]
MOLFESD	free energy surface densities	MLR	[62–64]
	Topology		
–	graph-theoretic descriptors	MLR	[66]
MLOGP	Σ hydrophob. atoms, Σ hydrophil. atoms, unsat. bonds, amphot. propert., proximity effects, special functionalities	MLR	[67]
VLOGP	electrotopological state (E-values), size-corrected E-values, topological shape descriptors	MLR	[68, 69]
T-LOGP	uniform-length descriptors	PLS	[70]
–	indicators for presence/absence of atom and bond types	NN	[72]
AUTOLOGP	4 autocorrelation vectors encoding hydrophobicity, molar refractivity, H-bonding acceptor and donor ability	NN	[73]
SciLogP	2D-descriptors according to Kier and Hall	NN	–
	Molecular properties		
BLOGP	μ, indicator for alkanes, charges on N, charges on O, MW, surface, ovality, number of C atoms	MLR	[71, 79]
–	cavity-, polarizability-, hydrogen bonding-term	MLR	[80]
–	MW, heat of formation, SASA, LUMO energy	MLR	[81]
–	surface area-, electrostatic potential-, charge transfer interaction-term	MLR	[82]
QLOGP	size, N (relat. to H-bonding), correction for alkanes	MLR	[83]
ASCLOGP	approximate surface calculations	MLR	[86, 87]
HYDRO	empirical solvation potentials	MLR	[88]
WHIM/logP	surface properties related to H-bonding and hydrophobicity	PLS	[84, 85]
–	GRID water probe, VolSurf parameters	PLS	[89]
–	GRID water probe	PLS	[90]
–	HINT hydrophobic fields	PLS	[91]
–	μ, indicator for alkanes, charges on N, charges on O, MW, surface, ovality, number of C atoms	NN	[92]
–	solvation energy, flexibility, Mulliken charges, electrostatic potentials, μ, polarizability, surface area, volume	NN	[93]
–	μ, indicator for alkanes, charges on N, charges on O, MW, surface, ovality, number of C atoms	NN	[94]
–	electrostatic potentials, total dipole moments, mean polarizabilities, surfaces, volumes, charges	NN	[95]

Programs given in bold and italic are commercially available; remaining are available from the authors. MLR = multiple linear regression; PLS = partial least squares; NN = neural networks

energy surface density' (FESD) concept was developed. The surface integral can be linearly related with experimental log P data.

Molecular hashkeys represent molecular surface properties as a linear array of pairwise surface-based comparisons of the target molecule against a common basis set of molecules [65]. Using a simple machine-learning technique (K nearest neighbor classifier) these hashkeys can be used to predict log P values.

Whole molecule approaches: topological indices

Topology concerns properties and spatial relations unaffected by continuous change of shape or size. In relation to molecules, connectivity deals with which atoms are connected to which other atoms. Since this is one unambiguous feature of well-defined molecules, molecular connectivity indices may be deduced directly from molecular structure and used to predict log P.

An example of this approach is the paper of Niemi et al. [66], who calculated graph-theoretic descriptors for a quite large database of 4076 molecules taken from the Pomona Starlist. The procedure first classified the chemicals into 14 groups based on the number of hydrogen bonds. Multiple regression analysis was then used to predict log P within the groups. For the combined datasets a standard error of estimates of 0.69 and an explained variance of 70.2% were found. Applying CLOGP, version 3.2, yielded values of 0.68 and 80.8%.

MLOGP – Multiple regression analysis of a set of 1230 organic molecules including general aliphatic, aromatic, and heterocyclic compounds together with complex drugs and agrochemicals was used by Moriguchi et al. [67] to derive their 'simple method' of calculating log P. Their final regression equation involved 13 parameters, including summation of hydrophobic atoms, summation of hydrophilic atoms, proximity effects, unsaturated bonds, amphoteric properties and specific functionalities such as the presence of a quaternary nitrogen, the number of nitro groups, or a dummy for the presence of β-lactam. An acceptable correlation coefficient of 0.952 was obtained; log P of the 1230 compounds was calculated with a standard deviation of ± 0.411. Examples for shortcomings are given, which however also occurred in comparative CLOGP calculations.

VLOGP – Gombar and Enslein [68, 69] introduced the VLOGP-approach, which employs electrotopological state values (E values), size-corrected E values and topological shape descriptors. For 6675 compounds from the Pomona Starlist, a 363-variable model was developed. Explained variance amounted to 98.5% and a standard error of estimate of 0.201 was calculated. A helpful feature of VLOGP is the definition of an optimum prediction space; it allows an a priori identification of compounds for which the model should not be applied.

T-LOGP – Junghans and Pretsch [70] describe the estimation of log P from a reference database using local predictive models. Structures are represented by uniform-length vectors generated from 3D-structures and substructures. A global model is built from all entries in the database using PLS, and in addition, individual local models are derived for each structure cluster by complete-linkage clustering. The authors use a dataset of 245 structures from [71]; 123 compounds for the training set and the remaining 122 for testing. The quality of prediction depends on the presence of a chemically similar compound in the training set, enabling the use of the appropriate local model; otherwise, a less accurate prediction is possible with the global model.

In some whole molecule approaches using topological descriptors [72–75], the prediction of log P is performed using artificial neural networks.

The model of Schaper and Samitier [72] is developed from a training set of 268 compounds with 147 descriptors (binary variables indicating the presence or absence of atom and bond types) with a network having 448 weights; standard deviation amounts to 0.25 for the training set and 0.66 for the test set of 50 compounds.

AUTOLOGP – Devillers et al. [73] use a new autocorrelation method combining a topological and physicochemical description. Molecules in their database are described by means of four different autocorrelation vectors encoding hydrophobicity, molar refractivity, H-bonding acceptor ability and H-bonding donor ability. The model is developed from a remarkable training set of 7200 compounds with 35 descriptors; the network has 1185 weights; a standard deviation of 0.37 for the training set and 0.39 for the test set of 519 compounds indicates good statistical performance. Devillers et al. [73] compare their approach with that of Schaper and Samitier [72], which performs better for

their training set of 268 structures, while the model of Devillers et al. [73] gives better estimates for the 50 compounds of Schaper's test set. This could indicate an overfitting of the training data in the latter approach and explain a reduced predictivity for compounds outside the training set.

SciLogP ULTRA – Another neural net approach using 2D-descriptors according to Kier and Hall was developed by Scivision company and is unfortunately not published. 8837 compounds with molecular weights from 21 to 821 from the Pomona starlist database were used as training set.

Huuskonen et al. [74] used neural networks based on atom-type electrotopological state indices using 326 compounds. Molecular weights and 32 atom-type E-state descriptors were analysed using multiple linear regression and artificial neural networks in comparison. To an enlarged training set (n = 1754) Huuskonen et al. [75] applied an extended set of 38 E-state indices with a more detailed description of amino, carbonyl, and hydroxy groups as inputs in 39-5-1 artificial neural networks ($r^2 = 0.90$ and RMS LOO = 0.46). For a test set of 116 structures not included in the training set a predictive r^2 of 0.94 and an RMS of 0.41 were calculated with neural nets. In this study prediction ability of artificial neural networks is superior to multilinear regression. The authors attribute this finding to the non-linear properties of neural nets allowing the detection of high-order relationships between E-state indices and log P.

Whole molecule approaches: molecular properties

Increasing speed and accuracy of molecular orbital calculations allow the derivation of models based on quantum chemical approaches. Accordingly, a variety of quantum chemical descriptors is used to model log P.

Rogers and Cammarata [76] measured log P for 19 aromatics and could correlate experimental log P with the superdelocalizability and charge density of their test compounds. Hopfinger and Battershall [77] developed a 'solvent-dependent conformational analysis procedure' (SCAP) which is based on the hydration shell model proposed by Hopfinger. For 20 simple organics the correlation of the SCAP-derived data with experimental log P was comparable in quality to correlation with Hansch's π-data. Klopman and Iroff [78] presented a charge density method using MINDO/3 and Hückel-type calculations based primarily on topology. For a set of 61 simple organics the results were favorably compared with those obtained with fragment analysis.

BLOGP – The group of Bodor [71, 79] started from the above noted Klopman's method with an attempt to bypass some shortcomings observed in the latter. Klopman's method was applicable only to compounds containing C, H, N and O atoms and only standard molecular geometry was used for MINDO/3 calculations. In addition, the calculated charge distribution alone seemed to be insufficient to characterize compound solubility. Accordingly, Bodor et al. [79] also examined the contribution of volume, surface, shape and dipole moment. The dataset of Klopman was enlarged to 118 molecules for which fully optimized geometries were obtained from AM1-calculations. Bodor and Huang [71] published an extended version of the AM1-method, in which the number of carbon atoms, the sum of the absolute values of atomic charges on each atom and the fourth power of the ovality were introduced as additional parameters. For a dataset of 302 molecules a regression equation with 17 parameters and r = 0.978 was derived.

Theoretical descriptors derived from the molecular surface area and the electrostatic potential were used by Haeberlein and Brinck [80] to predict log P. An *ab initio* SCF approach was used to compute the molecular descriptors at the HF/6-31G* level. Only three theoretical parameters – a cavity term, a dipolarity/polarisability term and a hydrogen bonding term – were needed for the correlation within a test set of 74 compounds. Predictions for 6 biologically active molecules differed from experimental log P by at most 0.51 units.

Makino [81] applied computer calculated molecular descriptors to a database of 139 polychlorinated biphenyls. The descriptors molecular weight, heat of formation, SASA and LUMO energy were most significant to predict log P of the dataset as shown by multiple linear regression analysis ($r^2 = 0.954$).

Sasaki et al. [82] presented a model using molecular surface area, electrostatic potentials and charge transfer interactions terms. Estimated log P values for 63 small organic molecules gave a correlation coefficient of 0.983 with a standard deviation of 0.260. Application of the model to 27 more complicated structures and comparison with the corresponding CLOGP data showed that CLOGP was superior, although the latter could not calculate all structures, which is typi-

cal of several fragmental methods.

QLOGP – A 'Molecular Size-Based Approach' was recently published by Bodor and Buchwald [83]. The authors used an algorithm combining analytical and numerical techniques to compute van der Waals volume and surface area. Only one additional parameter was necessary to adequately describe log *P* in a diverse test set of 320 molecules. This parameter, labelled *N*, is a positive integer increased in an additive manner by each functional group within a test molecule. The authors hypothesize that *N* could be related to the hydrogen bonds formed at the acceptor sites of the solute molecule when it is transferred from octanol to water. By adding a correction which reflects the peculiar partitioning behaviour of alkanes, Bodor and Buchwald derived with these three parameters a final model for training test set with r = 0.989 and s = 0.214. The predictive power of their model was tested using a validation set of 438 molecules comprising such diverse structures as hydrogen and prednisolone. An r of 0.975 and a standard deviation of 0.365 indicate the validity of the model.

ASCLOGP – Conformation dependent log *P* values may be obtained by approximate surface calculations using the program ASCLOGP introduced by Ulmschneider [84, 85]. This model is based on the separate calculation of s and p partial atomic surfaces. However, it was not persued any further.

HYDRO – Richards and Williams [86] developed the HYDRO program for computing conformation-dependent lipophilicity of flexible molecules. Their approach combines stochastic sampling methods with empirical solvation potentials. For a set of dipeptides these authors could show that excellent estimates of log *P* can be obtained for flexible amphiphilic structures which are able to adopt very different conformational distributions in water and octanol. Their work also appears to confirm that the neglect of conformational effects underlies the failure of substructure approaches to yield accurate log *P* estimates for flexible amphiphilic structures.

MS-WHIM/logP – MS-WHIM descriptors [87] were developed to capture global three-dimensional chemical information at the molecular surface level. Initially they encoded information on size, shape and electrostatic distribution of a molecule. More recently they were enriched introducing new molecular surface properties related to hydrogen bonding capacity and hydrophobicity. These expanded MS-WHIM descriptors were applied to a set of 268 small molecules to test their ability to predict log *P* [88]. The best PLS model has three latent variables, an r^2 of 0.771 and a q^2 of 0.709. However, a relatively larg standard deviation (SDEP = 0.659) was observed.

In the following some whole molecule approaches [89–95] are described, which also use molecular properties, but apply PLS analysis [89–91] or neural networks [92–95] for validating the predictions.

GOLPE/logP – The method of Cruciani et al. [89] uses a 'dynamic physicochemical interaction model' to evaluate the interaction energies of the water solvent with the hydrophilic and hydrophobic regions of the solute. In a first step the compounds are described with the GRID force field using the water probe. In the next phase the maps are transformed into two-dimensional physicochemical descriptors by the VolSurf program. Then, the PLS option of the GOLPE software is used to correlate the VolSurf parameters with the experimental log *P* of the test compounds. Finally, this model is used to predict the log *P* for new compounds.

Quite comparable methodological strategies, using CoMFA instead of GOLPE, were applied by Kim [90] to 17 furans and 54 triazines and by Waller [91] to 24 polyhalogenated aromatics and heteroaromatics.

Four papers will be discussed that use neural networks (NN) to predict log *P* [92-95]. Bodor et al. [92] and Breindl et al. [95] compare the results of the NN technique with those of multiple linear regression (MLR). All publications used a two-layer feed-forward NN with supervised learning by the backpropagation algorithm. Thus, they have the same level of technology. The size of the dataset ranges from 321 [92–94] to 1085 [95] compounds. [92–94] use the same dataset. Thus, the results of these studies can be directly compared. The larger the dataset, the more remarkable is the corresponding work, as then a broader scope of the respective prediction method can be anticipated. In some cases [92, 93] no clear information is given on the separation of the database into training and test sets. The descriptors are derived from semi-empirical quantum-mechanical calculations. The greater the number of descriptors used in a modeling technique such as statistical methods or NN, the greater is the risk of overdetermining the model and thus losing predictivity. The publications discussed here are quite comparable as they include similar numbers of descriptors. The number of descriptors also

determines the size of the NN architecture and thus the number of weights that must be determined in the learning phase. The larger the ratio of weights to input data, the less robust is the predictivity.

The model of Bodor et al. [92] is developed from a training set of 302 compounds with 17 descriptors from AM1 calculations with a network having 58 weights. The standard deviation ($s = 0.28$) is slightly better than that obtained by MLR (0.31). The test set of 21 compounds gives an s of 0.44 (MLR: $s = 0.38$).

Quite similar results to [92] were obtained by Grunenberg and Herges [93] with the same dataset; descriptors from AM1 calculations could be reduced from 17 to 11 and the network has 40 weights instead of 58. A standard deviation of 0.31 for the training set and of 0.29 for the test set of 21 compounds is observed.

Also Duprat et al. [94] start with the same dataset as Bodor et al. [92]. Removing outliers and selection of descriptors by Gram-Schmidt orthogonalization leads to 250 compounds in the training set. 6 descriptors were selected; the network has 56 weights, $s = 0.35$ for the training set and $s = 0.30$ for the test set ($n = 48$).

Breindl et al. [95] work with a significantly larger training set of 980 compounds. Corresponding data for this paper are: 16 descriptors were derived from AM1 calculations; the network has 451 weights; the standard deviation amounts to 0.41 for the training set and 0.53 for the test set of 105 structures, which were obtained by random selection from 1085 compounds.

Above sections were dedicated to describe representatives of substructure approaches and whole molecule approaches for calculating log P. This overview is far from being complete. Instead, our main scope was to highlight the characteristics of the selected log P models and to discuss their advantages and disadvantages. A main goal of this summary is a classification of currently available log P porgrams according to their methodological background, as depicted in Table 3. Sources of the calculation programs are given in Table 4.

Predictive power of log *P* calculation approaches

The routine application of calculation procedures requires the comprehensive comparison of calculated with experimental log P. Some examples of such comparisons are listed in Table 5. Useful sets of experimental log P data are the Pomona Starlist [96] or the listing provided by Meylan and Howard as part of the KOWWIN software.

Linear regression analysis is preferentially used as statistical device for checking the predictive power of log P programs. Regression analysis, however, can appear to yield a good fit between calculation and experiment by producing a high correlation, which is actually due to equilibrated positive and negative deviations. Alternatives exist in using NN or PCA, which precisely unravels the comparability in absolute values and the compound ranking in the database. Further validity criteria might consist a) in calculating absolute residual sums, b) in counting acceptable ($\Delta < 0.5$), intermediate ($\Delta > 0.5$ and < 1.0) and unacceptable ($\Delta > 1.0$) differences between calculation and experiment or c) in plotting experimental data versus absolute errors of calculation [97].

In the following some papers will be described dealing with the predictive power of log P calculation approaches. The first section concerns studies exclusively focusing on substructure approaches, while the second considers comparisons including both substructure and whole molecule approaches.

Substructure approaches – An extensive comparison of several substructure approaches was performed by the group of Schüürmann [97, 98]. Datasets of 515 [97] and 650 [98] diverse compounds (drugs, agrochemicals, PCB's and simple organics) were calculated with CLOGP and the Ghose/Crippen, Suzuki/Kudo, Klopman and Broto approaches. In [98] the LOGKOW method was also included. The statistical results of a comparison with experimental data from the Pomona Starlist attribute highest quality to CLOGP [97] or CLOGP and LOGKOW [98]. One should note, however, that using data from the Starlist gives undue weights to the quality of CLOGP, because these compounds were in the test set used to calibrate CLOGP. A general observation, also made by [97, 98], concerns larger differences between measured and calculated log P for highly lipophilic compounds. It is difficult to decide whether this is due to reduced precision of experimental data or to a reduced quality of calculations in the high log P range.

An interesting comparison between CLOGP and ALOGP methods was performed by Ghose et al. [48]. Using experimental data from the Pomona Starlist, these authors observed a marginal superiority of CLOGP over ALOGP for the entire set, varying predictivity depending on the chemical subclasses inspected and a 'size-dependence' of the calculations

Table 3. Classification scheme for log *P* calculation programs.

Substructure approaches			
Fragmental methods		Atom contribution methods	
CLOGP		MOLCAD	(Crippen original)
Σf–SYBYL	(Rekker-type)	TSAR	(Crippen original)
PROLOGP_cdr	(Rekker-type)	PROLOGP_atom	(Crippen original)
SANALOGP_ER	(Rekker-type)	ALOGP98	(Crippen revised)
KLOGP		SMILOGP	
KOWWIN		XLOGP	
ACD/LogP			
CHEMICALC			

Whole molecule approaches		
Mol. lipophilicity potential	Topological indices	Molecular properties
CLIP	MLOGP	BLOGP
HINT	AUTOLOGP	QLOGP
MOLFESD	VLOGP	
	T-LOGP	
	SciLogP ULTRA	

Log *P* calculation programs can be divided into two classes: Substructure approaches have in common that molecules are cut into groups (fragmental methods) or atoms (atom contribution methods). Fragmental methods use corrections except CHEMICALC. Atom contribution methods work without correction factors except XLOGP. The high quality of XLOGP and the limited predictivity of CHEMICALC underline the importance of using correc- tion rules. The almost identical methodological background of the fragmental methods Σf–SYBYL, PROLOGP_cdr and SANALOGP_ER as well as the atom contribution methods MOLCAD, TSAR and PROLOGP_atomics indicates their interchangeability.
Whole molecule approaches inspect the entire molecule; they use either molecular lipophilicity potentials (MLP), topological indices or molecular properties to quantify log *P*. The quite large number of attempts to model log *P* with molecular descriptors (see Table 2) sharply contrasts to the limited number of elaborated programs available. This is particularly true for whole molecule approaches using molecular properties (only 2 out of nearly 20), while almost all approaches using topological descriptors (5 out of 6) are commercially available. Due to the limited reliability of log *P* programs we recommend to use a diverse set of programs instead of a single procedure. Adequate selection is easily performed using this Table. It could comprise following programs: CLOGP, ACD/LogP (or KOWWIN), ALOGP98, XLOGP 2.0, CLIP, AUTOLOGP (or SciLogP) and QLOGP covering the entire spectrum of methodologies. Application of such a 'program set' would facilitate to judge the quality of the obtained results.

with CLOGP better calculating compounds in the range of up to 20 atoms, while ALOGP showed better accuracy for molecules with more than 45 atoms.

Another comparison [43] concerns the predictive performance of HLOGP, CLOGP and ALOGP. Evaluation of these methods was again based on functional group composition and size (atom count in a molecule). The test set consisted of 931 molecules which were not part of the training set for developing ALOGP and HLOGP. HLOGP in general offered better predictions than ALOGP and CLOGP. The observation that increasing size of a molecule worsens the predictivity of CLOGP [48] is confirmed in this paper. A weak dependence of predictivity on functional group composition and the ability to cope with longer-range interactions in an automated fashion are stated as advantages of HLOGP as compared to ALOGP and CLOGP. On the other hand, conjugation effects which propagate longer distances or the effects of folding a long chain are not accounted for by the holograms used in HLOGP.

Some comparisons of substructure approaches for small datasets of drugs and simple organics have been published [99–101]. These studies indicated a better predictivity of fragmental as compared to atom contribution methods.

Substructure and whole molecule approaches – In two papers the group of Bodor [12, 83] compared the predictive performance of QLOGP with several

Table 4. Sources of log *P* calculation programs.

Method	Software	Provider	Internet
ACD/LogP	ACD/LogP	Advanced Chemistry Development	www.acdlabs.com
ALOGP	Tsar	Oxford Molecular	www.oxmol.co.uk
	MOLCAD	Tripos	www.tripos.com
	PROLOGP	Compudrug	www.compudrug.com/
ALOGP98	ALOGP98	Cerius-2 / MSI	www.msi.com
AUTOLOGP	AUTOLOGP	Devillers	jde-ctis@imaginet.fr
CLIP	CLIP	Testa, Carrupt	bernard.testa@ict.unil.ch
CLOGP	MedChem	Daylight	www.daylight.com
		Biobyte	www.biobyte.com
HINT	HINT	Edusoft	eslc@vabiotech.com
KLOGP		Multicase, Klopman	gxk6@po.cwru.edu
		Charles River	
LOGKOW	KOWWIN	Syracuse Research corporation (SRC)	meylan@syrres.com
PrologP	PrologP	Compudrug	aidacitti@comgenex.com
SciLogP	SciQSAR	SciVision	www.scivision.com
	SciLogP		
TLOGP	TLOGP	Upstream Solutions	www.upstream.ch
VLOGP	Topkat	Oxford Molecular	www.oxmol.co.uk
XLOGP	XLOGP	Lai	lai@ipc.pku.edu.cn

substructure approaches. For 105 drugs and simple organics [83] QLOGP performed almost as well as Σf and CLOGP and was superior to the Ghose/Crippen and Suzuki/Kudo methods. For 145 drugs, peptides and nucleosides [12] QLOGP was compared with Σf, CLOGP, KLOGP, LOGKOW and ACD/LogP. LOGKOW and ACD/LogP were ranked best, but QLOGP was close to the best programs.

Moriguchi et al. [102] published a comparative study using the same 22 drugs as tested in [100]. Their MLOGP approach scored better than Σf, CLOGP and the Suzuki/Kudo method. In contrast to the other methods, no differences to experimental log *P* of more than 2 log units were observed.

Viswanadhan et al. [103] assessed the predictive power of BLOGP, CLOGP and the Ghose/Crippen approach for 47 nucleosides and nucleobases and found the latter to be best for this class of structures, which is miscalculated by many calculation programs. Gombar and Enslein [68] used the same data set and also included VLOGP, which showed the best fit to measured log *P* among these five methods.

Devillers [104] compared the performances of a log *P* model designed from EVA (Eigen VAlue) descriptors based on theoretically derived normal coordinate frequencies and using PLS for validation with a neural network model employing autocorrelation vectors for molecule description. The superiority of the latter was found for a test set of 50 molecules as demonstrated by rms values of 0.88 and 0.30, respectively.

Petrauskas and Kolovanov [105] used the drug subset (n = 48) of Mannhold and Dross [106] to compare the ACD/LogP approach with SciLogP ULTRA. ACD/LogP performs better (r = 0.986, s = 0.26) than SciLogP ULTRA (r = 0.925, s = 0.59). In addition, it is demonstrated that various structural effects like long chains, inductive and resonance interactions as well as hydrogen bonding are more correctly treated by ACD/LogP.

Mannhold et al. [106–108] tested 14 calculation programs for their predictive power with a database of 160 compounds including simple organics and drugs. Fragmental methods scored best, followed by atom-based and whole molecule approaches. However, since no comprehensive study of the latter was made, their validity remains to be clarified. Out of the entire database a balanced set (n = 55), was selected and investigated with the PCA option of the GOLPE program [108]. The loading plot of the first versus the second component (Fig. 1) gives an overview of the quality of the calculation procedures: fragmen-

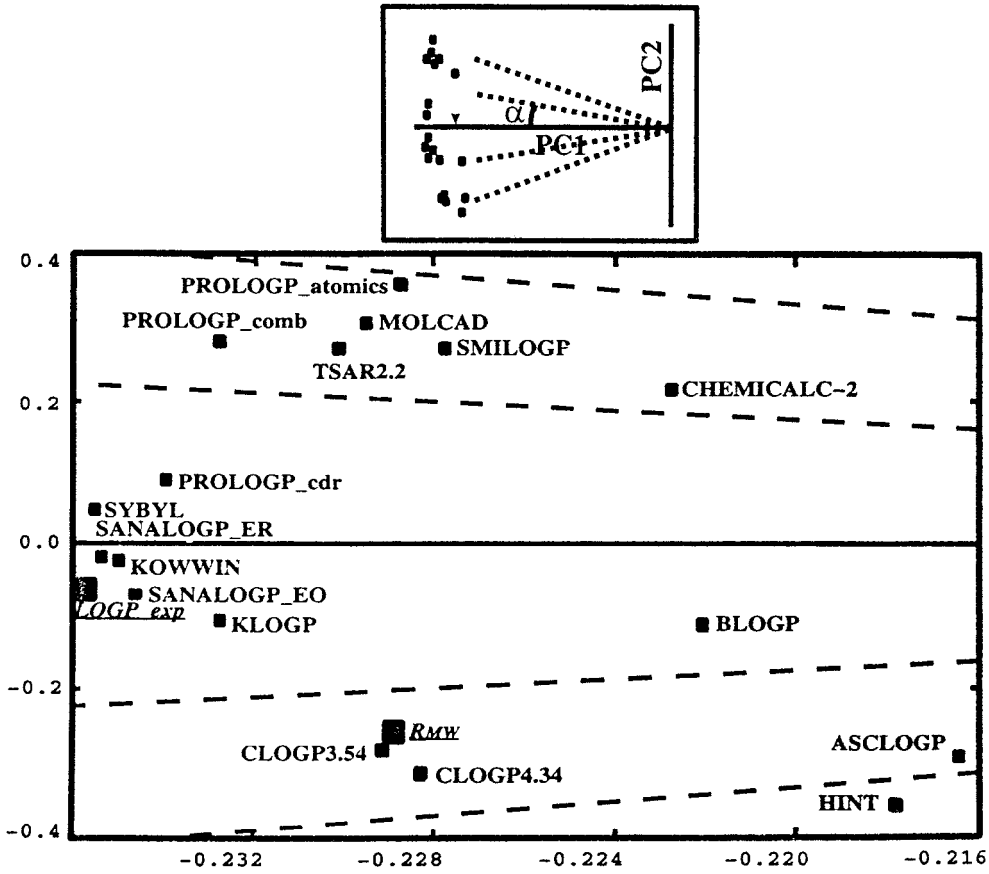


Figure 1. Comparison of 14 calculation procedures by principal component analysis (loading plot of the first versus the second component). The information content is twofold: (1) the distance between the projection of the data points for experimental and calculation methods onto the first component indicates the similarity in absolute values for experiment and calculation; (2) the deviation of the loading direction of a given variable from the direction of the first component indicates the similarity between a calculation and experiment in reflecting the compound ranking in log P data within a database. Figure is taken from ref. [108] with kind permission of the copyright owners.

tal methods compare most favorably to experimental log P and also capture the compound ranking in log P data similar to the experimental approaches. Comparability of absolute values and of compound ranking are slightly less for atom-based methods and CLOGP. This tendency is even more pronounced for the whole molecule approaches, with the exception of BLOGP, which captures the compound ranking almost as well as fragmental methods, while the comparability in absolute values is limited, indicating some systematic error in this approach.

Petrauskas and Kolovanov [40] and Wang et al. [52] also used our dataset [106] to compare their approaches ACD/LogP and XLOGP 2.0 with 14 calculation programs tested in [106]. Both groups could show the top-scoring quality of their programs in comparison with this broad spectrum of competitors.

Comparisons of the predictive power of calculation procedures are by their nature limited. Studies suffer from a limited number of programs investigated and/or a limited number and diversity of structures included. In addition, comparisons often focus on substructure methods and pay less attention to whole molecule methods. Finally, programs develop; newer versions may have improved considerably. Nevertheless, some cautious evaluations seem to be possible. Criteria of comparison should be *precision, general applicability* and *speed*.

Regarding *precision* current comparisons attribute highest quality to fragmental methods; the newer approaches LOGKOW and ACD/Log P seem to be superior to Σf, CLOGP and KLOGP. An interesting aspect is the possibility that precision varies with the chemical structures under investigation. Thus, the

Table 5. Studies on the predictive power of log *P* calculation approaches.

Included methods	Database content	n	Ref.
Substructure approaches			
CLOGP, GC, SK, KLOGP, B	drugs, agrochemicals, PCB's, simple organics	515	[97]
CLOGP, **LOGKOW**, GC, SK, KLOGP, B	drugs, agrochemicals, PCB's, simple organics	650	[98]
CLOGP, ALOGP	Pomona starlist	1813	[48]
HLOGP, CLOGP, ALOGP	drugs	931	[43]
CLOGP, **Σ *f***, GC, SK	drugs	22	[100]
Substructure and whole molecule approaches			
Σ *f*, **CLOGP**, QLOGP, GC, SK	drugs, simple organics	105	[83]
LOGKOW, **ACD/LogP**, QLOGP, Σf, CLOGP, KLOGP	drugs, peptides, nucleosides	145	[12]
MLOGP, Σf, CLOGP, SK	drugs	22	[102]
GC, BLOGP, CLOGP, KLOGP	nucleosides, nucleobases	47	[103]
VLOGP, BLOGP, CLOGP, KLOGP, GC	nucleosides, nucleobases	47	[68]
AUTOLOGP, EVA/logP	simple organics	50	[104]
ACD/LogP, SciLogP ULTRA	drugs	48	[105]
LOGKOW, Σf, CLOGP, KLOGP, GC, SK, SMILOGP, BLOGP, ASCLOGP, HINT	drugs, simple organics	138	[106]
ACD/LogP, **LOGKOW**, Σf, CLOGP, KLOGP, GC, SK, SMILOGP, BLOGP, ASCLOGP, HINT	drugs	48	[40]
LOGKOW, **XLOGP**, Σf, CLOGP, KLOGP, GC, SK, SMILOGP, BLOGP, ASCLOGP, HINT,	drugs, simple organics	138	[52]

Calculation methods given in bold under 'included methods' scored best in the respective validation study. Abbreviations: ACD/LogP = Petrauskas; ASCLOGP = Ulmschneider; AUTOLOGP = Devillers; B = Broto; BLOGP = Bodor; CLOGP = Hansch/Leo; GC = Ghose/Crippen; HINT = Kellogg/Abraham; K = Klopman; LOGKOW = Meylan/Howard; QLOGP = Buchwald/Bodor; SciLogP ULTRA = SciVision; Σf = Rekker; SK = Suzuki/Kudo; SMILOGP = Dubost; XLOGP = Lai

chemical composition of a database could guide the choice of the calculation program. It has to be emphasized, however, that these first hints (such as Σf for simple organics, VLOGP for nucleosides, Makino approach for polyhalogenated structures) need to be substantiated by investigations of larger databases.

General applicability is limited for most fragmental methods due to missing parametrization, in particular for the Rekker-type approaches. The situation is less critical for LOGKOW, ACD/LogP and CLOGP from version 4.0 on. In contrast to substructure methods, several programs of whole molecule approaches always work (such as MLOGP and some neural network approaches), but may be less reliable for certain classes of compounds.

Regarding *speed* of calculation, substructure methods again surpass many whole molecule approaches. In particular, methods based on quantum chemical calculations ask for more computation time.

Taken together, calculation of log *P* continues to be of outstanding importance in drug research. Currently available calculation programs, however, are far from being perfect and invite to further improve the existing and to develop new approaches. Considering the limited reliability of calculation programs we urgently recommend to use a diverse set of programs instead of a single procedure. Adequate selection is easily performed inspecting Table 3. It could comprise following programs: CLOGP, ACD/LogP (or KOWWIN), ALOGP98, XLOGP 2.0, CLIP, AUTOLOGP (or SciLogP) and QLOGP covering the entire spectrum of methodologies. The application of such a 'program set' would facilitate to judge the quality of the obtained results.

Acknowledgement

We would like to thank Johnny Gasteiger for valuable comments on some NN-validated approaches.

References

1. Sangster, J., Octanol-Water Partition Coefficients: Fundamentals and Physical Chemistry. Wiley Series in Solution Chemistry, Vol. 2, Wiley, New York, NY, 1997.
2. Pliska, V., Testa, B. and van de Waterbeemd, H. (Eds.) Lipophilicity in Drug Action and Toxicology. Methods and Principles in Medicinal Chemistry, Vol. 4, VCH Publishers, Weinheim, 1996.
3. Carrupt, P.-A., Testa, B. and Gaillard, P., in Lipkowitz, K.B. and Boyd, D.B. (Eds), Reviews in Computational Chemistry, Vol. 11, Wiley-VCH, 1997, pp. 241–315.
4. Fujita, T., Iwasa, J. and Hansch, C., J. Am. Chem. Soc., 86 (1964) 5175–5180.
5. Nys, G.G. and Rekker, R.F., Chim. Ther., 8 (1973) 521–535.
6. Nys, G.G. and Rekker, R.F., Chim. Ther., 9 (1974) 361–375.
7. Rekker, R.F., A means of characterizing membrane systems. Pharmacochem. Library Vol. 1, Elsevier, Amsterdam, 1977.
8. Rekker, R.F. and de Kort, H.M., Eur. J. Med. Chem., 14 (1979) 479–488.
9. Broto, P., Moreau, G. and Vandycke, C., Eur. J. Med. Chem., 19 (1984) 71–78.
10. Dearden, J.C., Environ. Health Perspect., 61 (1985) 203–228.
11. van de Waterbeemd, H. and Testa, B., Adv. Drug Res., 16 (1987) 85–225.
12. Buchwald, P. and Bodor, N., Curr. Med. Chem., 5 (1998) 353–380.
13. Testa, B. and Seiler, P., Arzneim. Forsch., 31 (1981) 1053–1058.
14. Raevsky, O.A., Schaper, K.J. and Seydel, J.K., Quant. Struct.-Act. Relat., 14 (1995) 433–436.
15. Raevsky, O.A., Schaper, K.J., van de Waterbeemd, H. and McFarland, J.W., 12th Eur. Symp. on Structure-Activity Relationships (1999) O22.
16. Kamlet, M.J., Abboud, J.L. and Taft, R.W., J. Am. Chem. Soc., 99 (1977) 6027–6038.
17. Taft, R.W., Abboud, J.-L.M., Kamlet, M.J. and Abraham, M.H., J. Sol. Chem., 14 (1985) 153–186.
18. Kamlet, M.J., Doherty, R.M., Carr, P., Abraham, M.H., Marcus, Y. and Taft, R.W., J. Phys. Chem., 92 (1988) 5244–5255.
19. Leahy, D.E., J. Pharm. Sci., 75 (1986) 629–636.
20. Leahy, D.E., Morris, J.J., Taylor, P.J., and Wait, A.R., J. Chem. Soc. Perkins Trans., 2 (1992) 723–731.
21. Meyer, P. and Maurer, G., Ind. Eng. Chem. Res., 34 (1995) 373–381.
22. Abraham, M.H. and Chadha, A.S., In Pliska, V., Testa, B. and van de Waterbeemd, H. (Eds), Lipophilicity in Drug Action and Toxicology, Methods and Principles in Medicinal Chemistry, Vol. 4, VCH Weinheim, 1996, pp. 311–337.
23. El Tayar, N., Testa, B. and Carrupt. P.A., J. Phys. Chem., 96 (1992) 1455–1459.
24. Masuda, T., Jikihara, T., Nakamura, K., Kimura, A., Takagi, T. and Fujiwara, H., J. Pharm. Sci., 86 (1997) 57–63.
25. Richards, N.G.J., Williams, P.B. and Tute, M.S., Int. J. Quant. Chem: Quant. Biol. Symp., 18 (1991) 299–316.
26. Richards, N.G.J., Williams, P.B. and Tute, M.S., Int. J. Quant. Chem., 44 (1992) 219–233.
27. Leo, A.J., Jow, P.Y.C., Silipo, C. and Hansch, C., J. Med. Chem., 18 (1975) 865–868.
28. Hansch, C. and Leo, A.J., Substituent Constants for Correlation Analysis in Chemistry and Biology. Wiley, New York, NY, 1979.
29. Leo, A.J., J. Pharm. Sci., 76 (1987) 166–168.
30. Leo, A.J., Methods Enzym., 202 (1991) 544–591.
31. Leo, A.J., Chem. Rev., 93 (1993) 1281–1306.
32. Chou, J.T. and Jurs, P.C., J. Chem. Inf. Comput. Sci., 19 (1979) 172–178.
33. Leo, A.J. and Hoekman, D., Perspect. Drug Discov. Des., 18 (2000) 19–38.
34. Rekker, R.F. and Mannhold, R., The Hydrophobic Fragmental Constant Approach. VCH, Weinheim, 1992.
35. Mannhold, R., Rekker, R.F., Dross, K., Bijloo, G., de Vries, G., Quant. Struct.-Act. Relat., 17 (1998) 517–536.
36. Darvas, F., Erdoz, I. and Teglas, G., in Hadzi, E. and Jerman-Blazic, B. (Eds.), QSAR in Drug Design and Toxicology, Elsevier, Amsterdam, 1987, pp. 70–73.
37. Petelin, D.E., Arslanov, N.A., Palyulin, V.A. and Zefirov, N.S., Proceedings of the10th European Symposium on Structure-Activity Relationships, Prous Sience Publishers, Barcelona, Spain, 1995, abstract B263.
38. Klopman, G., Li, J.W., Wang, S. and Dimayuga, M., J. Chem. Inf. Comput. Sci., 34 (1994) 752–781.
39. Meylan, W.M. and Howard, P.H., J. Pharm. Sci., 84 (1995) 83–92.
40. Petrauskas, A.A. and Kolovanov, E.A., Perspect. Drug Discov. Design, 19 (2000) 99–116.
41. Petrauskas, A.A. and Kolovanov, E.A., ACD Approaches For PHYS-Chem Data Prediction. 13th Eur. Symp. Quant. Struct.-Act. Relat., abstr. book P.4, Düsseldorf (2000).
42. Suzuki, T. and Kudo, Y., J. Comput. Aided Mol. Des., 4 (1990) 155–198.
43. Viswanadhan, V.N., Ghose, A.K. and Wendoloski, J.J., Perspect. Drug Discov. Des., 19 (2000) 85–98.
44. Ghose, A.K. and Crippen, G.M., J. Comp. Chem., 7 (1986) 565–577.
45. Ghose, A.K. and Crippen, G.M., J. Chem. Inf. Comp. Sci., 27 (1987) 21–35.
46. Ghose, A.K., Pritchett, A. and Crippen, G.M., J. Comp. Chem. 9 (1988) 80–90.
47. Viswanadhan, V.N., Ghose, A.K., Revankar, G.R. and Robins, R.K., J. Chem. Inf. Comput. Sci., 29 (1989) 163–172.
48. Ghose, A.K., Viswanadhan, V.N. and Wendoloski, J.J., J. Phys. Chem., A102 (1998) 3762–3772.
49. Wildman, S.A. and Crippen, G.M., J. Chem. Inf. Comput. Sci., 39 (1999) 868–873.
50. Convard, T., Dubost, J.P., Le Solleu, H. and Kummer, E., Quant. Struct.-Act. Relat., 13 (1994) 34–37.
51. Wang, R., Fu, Y. and Lai, L., J. Chem. Inf. Comp. Sci., 39 (1999) 868–873.
52. Wang, R., Gao, Y. and Lai, L., Perspect. Drug Discov. Des., 19 (2000) 47–66.
53. Audry, E., Dubost, J.-P., Colleter, J.-C. and Dallet, P., Eur. J. Med. Chem., 21 (1986) 71–72.
54. Fauchère, J.-L., Quarendon, P. and Kaetterer, L., J. Mol. Graphics, 6 (1988) 203–206.
55. Furet, P., Sele, A. and Cohen, N.C., J. Mol. Graphics, 6 (1988) 182–189.

56. Gaillard, P., Carrupt, P.-A., Testa, B. and Boudon, A., J. Comput.-Aided Mol. Design, 8 (1994) 83–96.
57. Kellogg, G.E., Semus, S.F. and Abraham, D.J., J. Comput. Aided Mol. Des., 5 (1991) 545–552.
58. Kellogg, G.E., Joshi, G.J. and Abraham, D.J., Med. Chem. Res., 1 (1992) 444–453.
59. Abraham, D.J. and Kellogg, G.E., J. Comput. Aided Mol. Des., 8 (1994) 41–49.
60. Kellogg, G. E. and Abraham, D. J., Analysis, 2 (1999) 19–23.
61. Kellogg, G. E. and Abraham, D. J., Eur. J. Med. Chem., 35 (2000) 651–661.
62. Heiden, W., Moeckel, G. and Brickmann, J., A new approach to analysis and display of local lipophi- licity/hydrophilicity mapped on molecular surfaces. J. Comput. Aided Mol. Des., 7 (1993) 503–514.
63. Pixner, P., Heiden, W., Merx, H., Moeckel, G., Möller, A. and Brickmann, J., J. Chem. Inf. Comput. Sci., 34 (1994) 1309–1319.
64. Brickmann, J. and Jäger, R., Analysis, 2 (1999) 15–18.
65. Ghuloum, A.M., Sage, C.R. and Jain, A.N., J. Med. Chem., 42 (1999) 1739–1748.
66. Niemi, G.J., Basak, S.C., Veith, G.D. and Grunwald, G., Environ. Tox. Chem., 11 (1992) 893–900.
67. Moriguchi, I., Hirono, S., Liu, Q., Nakagome, I. Matsushita, Y., Chem. Pharm. Bull., 40 (1992) 127–130.
68. Gombar, V.K. and Enslein, K., J. Chem. Inf. Comput. Sci., 36 (1996) 1127–1134.
69. Gombar, V.K., SAR QSAR Environ. Res., 10 (1999) 371–380.
70. Junghans, M. and Pretsch, E., Fresenius J. Anal. Chem., 359 (1997) 88–92.
71. Bodor, N. and Huang, M.J., J. Pharm. Sci., 81 (1992) 272–281.
72. Schaper, K.-J. and Samitier, M.L.R., Quant. Struct.-Act. Relat., 16 (1997) 224–230.
73. Devillers, J., Domine, D., Guillon, C. and Karcher, W., J. Pharm. Sci., 87 (1998) 1086–1090.
74. Huuskonen, J.J., Villa, A.E. P. and Tetko, I.V., J. Pharm. Sci., 88 (1999) 229–233.
75. Huuskonen, J.J., Livingstone, D.J. and Tetko, I.V., J. Chem. Inf. Comput. Sci., 40 (2000) 947–955.
76. Rogers, K.S. and Cammarata, A., J. Med. Chem., 12 (1969) 692–693.
77. Hopfinger, A.J. and Battershell, R.D., J. Med. Chem., 19 (1976) 569–573.
78. Klopman, G. and Iroff, L.D., J. Comp. Chem., 2 (1981) 157–160.
79. Bodor, N., Gabanyi, Z. and Wong, C.K., J. Am. Chem. Soc., 111 (1989) 3783–3786.
80. Haeberlein, M. and Brinck, T., J. Chem. Soc., Perkin Trans., 2 (1997) 289–294.
81. Makino, M., Chemosphere, 37 (1998) 13–26.
82. Sasaki, Y., Kubodera, H., Matuszaki, T. and Umeyama, H., J. Pharmacobio-Dyn., 14 (1991) 207–214.
83. Bodor, N. and Buchwald, P., J. Phys. Chem., B101 (1997) 3404–3412.
84. Ulmschneider, M., Analytical Model for the Calculation of van der Waals and Solvent Accessible Surface Areas. Contribution to the Calculation of Free Enthalpies of Hydration and Octanol/Water Partition Coefficients. Ph.D. Thesis, University of Haute-Alsace, Mulhouse/France (1993).
85. van de Waterbeemd, H., Karajiannis, H., Kansy, M., Obrecht, D., Müller, K. and Lehmann, Ch., in Sanz, F., Giraldo, J., Manaut, F. (Eds.), QSAR and Molecular Modelling: Concepts, Computational Tools and Biological Applications. Prous, Barcelona; 1995, pp 78–90.
86. Richards, N.G.J. and Williams. P.B., Chem. Design Automat. News, 9 (1994) 21–26.
87. Bravi, G., Gancia, E., Mascagni, P., Pegna, M., Todeschini, R. and Zaliani, A., J. Comput. Aided Mol. Des., 11 (1997) 79–92.
88. Bravi, G. and Wikel, J.H., Quant.-Struct. Act.-Relat., 19 (2000) 39–49.
89. Cruciani, G., Clementi, S., Fravolini, A., Cecchetti, V., Tabarrini, O. and Filipponi, E., XIII. Meeting of the Italian Pharm. Chemistry Society, Paestum, Italy, 1996, abstr. book P 126.
90. Kim, K.H., J. Comp.-Aid. Design, 9 (1995) 308–318.
91. Waller, C.L., Quant. Struct.-Act. Relat., 13 (1994) 172–176.
92. Bodor, N., Huang, M.-J. and Harget, A., J. Mol. Struct. (Theochem), 309 (1994) 259–266.
93. Grunenberg, J. and Herges, R., J. Chem. Inf. Comput. Sci., 35 (1995) 905–911.
94. Duprat, A.F., Huynh, T. and Dreyfus, G., J. Chem. Inf. Comput. Sci., 38 (1998) 586–594.
95. Breindl, A., Beck, B., Clark, T. and Glen, R.C., J. Mol. Model., 3 (1997) 142–155.
96. Hansch, C., Leo, A. and Hoekman, D. (Eds.), Exploring QSAR; hydrophobic, electronic and steric constants. ACS Professional Reference Book, 1995.
97. Kühne, R., Rothenbacher, C., Herth, P. and Schüürmann, G., in Jochum, C. (Ed.), Software Development in Chemistry, Vol. 8, GDCh, Frankfurt, 1994, pp. 207–224.
98. Schüürmann, G., Kühne, R., Ebert, R.-U. and Kleint, F., Fresenius Environ. Bull., 4 (1995) 13–18.
99. Mannhold, R., Dross, K. and Rekker, R.F., Quant. Struct.-Act. Relat., 9 (1990) 21–28.
100. Rekker, R.F., Mannhold, R. and ter Laak, A.M., Quant. Struct.-Act. Relat., 12 (1993) 152–157.
101. Mannhold, R., Rekker, R.F., Sonntag, C., ter Laak, A.M., Dross, K. and Polymeropoulos, E.E., J. Pharm. Sci., 84 (1995) 1410–1419.
102. Moriguchi, I., Hirono, S., Nakagome, I. and Hirano, H., Chem. Pharm. Bull., 42 (1994) 976–978.
103. Viswanadhan, V.N., Reddy, M.R., Bacquet, R.J. and Erion M.D., J. Comp. Chem., 14 (1993) 1019–1026.
104. Devillers, J., Perspect. Drug Discov. Des., 19 (2000) 117–113.
105. Petrauskas, A.A. and Kolovanov, E.A., 13th Eur. Symp. Quant. Struct.-Act. Relat., abstr. book P.84, Düsseldorf (2000).
106. Mannhold, R. and Dross K., Quant. Struct.-Act. Relat., 15 (1996) 403–409.
107. van de Waterbeemd, H. and Mannhold, R., in Pliska, V., Testa, B. and van de Waterbeemd, H. (Eds.), Lipophilicity in Drug Action and Toxicology. Methods and Principles in Medicinal Chemistry, Vol. 4, VCH Publishers, Weinheim, 1996, pp. 401–418.
108. Mannhold, R., Cruciani, G., Dross, K. and Rekker, R.F., Comput. Aided Mol. Des., 12 (1998) 573–581.