Pharmaceutical Research, Vol. 13, No. 3, 1996

Commentary

Lipophilicity in Molecular Modeling

Bernard Testa,[1,2] Pierre-Alain Carrupt,[1] Patrick Gaillard,[1] Frédéric Billois,[1] and Peter Weber[1]

Received September 28, 1995; accepted November 28, 1995

Purpose. The molecular lipophilicity potential (MLP) offers a three-dimensional representation of lipophilicity, a molecular property encoding intermolecular recognition forces and intramolecular interactions.
Methods. The interest and applications of the MLP in molecular modeling are varied, as ilustrated here.
Results. The MLP is a major tool to assess the dependence of lipophilicity on conformation. As a matter of fact, the MLP combined with an exploration of the conformational space of a solute reveals its "chameleonic" behavior, i.e. its capacity to adapt to its molecular environment by hydrophobic collapse or hydrophilic folding. Another successful application of the MLP is its concatenation into 3D-QSAR (Comparative Molecular Field Analysis, CoMFA).
Conclusion. Work is in progress to expand the MLP into a docking tool in the modeling of ligand-receptor interactions.

KEY WORDS: lipophilicity; partition coefficients; intermolecular forces; intramolecular interactions; conformation; molecular lipophilicity potential; MLP; 3D-QSAR; comparative molecular field analysis (CoMFA); receptor docking.

INTRODUCTION

Since about one century, lipophilicity is recognized as a meaningful parameter in structure-activity relationship studies, and with the epoch-making contributions of Hansch has become the single most informative and successful physicochemical property in medicinal chemistry (1–3). Not only has lipophilicity found innumerable applications in quantitative structure-activity and structure-disposition relationships, but its study has revealed a wealth of information on molecular structure.

Lipophilicity is determined experimentally as partition coefficients (written as log P and valid only for a single chemical species) or as distribution coefficients (written as log D refering to a mixture of chemical species generally pH-dependent) (4). As such, lipophilicity measured under a set of well-defined conditions expresses a balance of intermolecular forces and intramolecular interactions whose understanding sheds light on biochemical recognition forces (5). For all above reasons, lipophilicity has become a major experimental and theoretical tool in drug design.

The single factor best accounting for the accelerated development of drug design in recent years is the explosive growth of molecular modeling as a branch of computational chemistry. The simulation of binding sites and their interactions with ligands (docking), the creation of three-dimensional QSAR (3D-QSAR) tools, and several other developments, have all contributed to bring drug design to a level of sophistication and command undreamed of a few years ago.

Interestingly, lipophilicity and molecular modeling have until recently remained separate tools. Molecular modeling is based on structural attributes (electronic properties, conformation, molecular fields, etc) obtained by computation, whereas lipophilicity is based (directly or indirectly) on experimental determinations and as such could not be integrated into molecular modeling. This situation has changed with the creation of lipophilicity potentials (6–12) where lipophilicity is computed in 3D-space from experimentally derived increments. This treatment allows experimental values to enter molecular modeling and bring additional information on intermolecular forces and intramolecular interactions. The fact that lipophilicity contains some information on the entropic components of such forces and interactions is particularly noteworthy.

This review presents the molecular lipophilicity potential (MLP) developed in our laboratory and its major applications in drug design. As we shall demonstrate, the MLP indeed opens new possibilities in molecular modeling and drug design.

INTERMOLECULAR FORCES AND INTRAMOLECULAR INTERACTIONS ENCODED IN LIPOPHILICITY

Before presenting the MLP, and in order to understand better its meaning and limitations, it is necessary to briefly recall the various forces and interactions that are implicitely expressed in lipophilicity.

Intermolecular Recognition Forces Encoded in Lipophilicity

As a ratio of two concentrations at saturation, the partition coefficient (log P) is the net result of all intermolecular forces

[1] Institute of Medicinal Chemistry, School of Pharmacy, BEP, University of Lausanne, CH-1015 Lausanne-Dorigny, Switzerland.
[2] To whom correspondence should be addressed.

0724-8741/96/0300-0335$09.50/0

between a solute and the two phases between which it partitions. Thus, when the solute elicits in the two solvents interactions of a given type (e.g. H-bond donation) which compensate each other, log P will contain no information about these interactions.

One highly informative interpretation of lipophilicity is based on its factorization of log P into a number of parameters (13), i.e.:

- π^*, a measure of the solute's dipolarity/polarizability and thus of its capacity to elicit orientation and induction forces;
- α and β, the solute's H-bond donor acidity and H-bond acceptor basicity, respectively;
- V, the molar or molecular volume which assesses the solute's capacity to elicit non-polar interactions, mainly hydrophobic and dispersion forces.

Thus, the octanol/water and the heptane/water partition coefficient can be expressed as (14):

$$\log P_{octanol} = 5.83(\pm0.53)\cdot V/100 - 0.74(\pm0.31)\cdot\pi^* - 3.51(\pm0.38)\cdot\beta - 0.15(\pm0.23)\cdot\alpha - 0.02(\pm0.34) \quad \text{(Eq.1)}$$

$$n = 78; \quad r^2 = 0.92; \quad s = 0.30; \quad F = 248$$

$$\log P_{heptane} = 6.78(\pm0.69)\cdot V/100 - 1.02(\pm0.39)\cdot\pi^* - 5.35(\pm0.50)\cdot\beta - 3.54(\pm0.30)\cdot\alpha - 0.06(\pm0.43) \quad \text{(Eq. 2)}$$

$$n = 75; \quad r^2 = 0.96; \quad s = 0.36; \quad F = 438$$

As a result of solvatochromic equations of this type, it is now common to factorize lipophilicity into two sets of terms, namely hydrophobicity which accounts for hydrophobic and dispersion forces, and polar terms which account for hydrogen bonds, and orientation and induction forces (4):

$$\text{Lipophilicity} = \text{Hydrophobicity} - \text{Polarity} \quad \text{(Eq. 3)}$$

Turning our attention to the major recognition forces of significance in molecular pharmacology and biology (Figure 1), we see that many of them are similar to the intermolecular forces expressed in lipophilicity. Only a limited number of recognition forces cannot find expression in lipophilicity as conventionally measured, namely ionic bonds, charge transfer interactions and aryl/aryl stacking interactions. The latter two would require an aromatic solvent, e.g. benzene or nitrobenzene, to be used in partitioning experiments. As for ionic interactions, they might perhaps be approachable in HPLC using an ionic stationary phase, but the problem of counterions and their influence is far from solved.

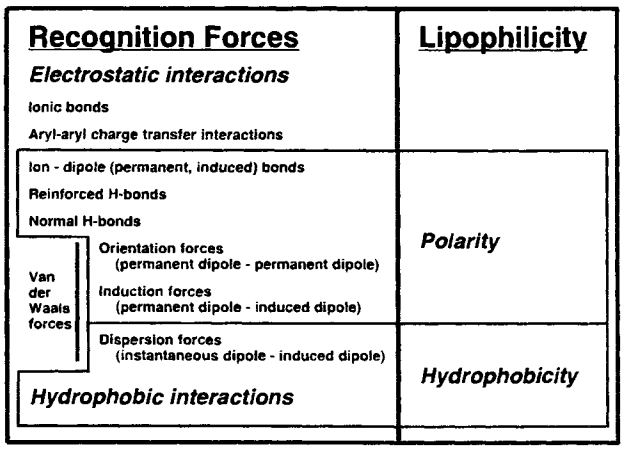


Fig. 1. A comparison between recognition forces in molecular pharmacology and biology (left panel) and intermolecular forces encoded in lipophilicity (right panel) (15).

Intramolecular Interactions Influencing Lipophilicity

Functional groups in solute molecules interact with each other in a number of ways depending on their own electronic and steric properties, on the number and nature of interconnecting bonds, and on intramolecular distances. Schematically, a number of dichotomic distinctions can be made, e.g. *electronic versus steric effects,* or *through-bond versus through-space interactions.* However, such distinctions may be misleading since they tend to neglect overlaps and intermediate cases.

One way by which intramolecular interactions can be considered is first for themselves, and then as influenced by isomerism and other aspects of molecular polymorphism. Intramolecular interactions considered for themselves can in turn be classified as follows (15):

A) Electronic Conjugations:

- *In aromatic systems:* Substituents in aromatic rings may influence each other in a number of ways depending on their chemical nature, mutual position, and the presence of other substituents.
- *Across aliphatic segments:* Interactions between functional groups separated by aliphatic segments can be caused by to a variety of through-space effects considered below, but in addition through-bond interactions may operate, e.g. via hyperpolarization.

B) Interactions Involving Polar Groups

- *Proximity effects between two neutral polar groups:* The proximity of two electronegative functionalities in a molecule increases the lipophilicity of the compound depending on the nature of the groups and their distance (2,16). These effects operate alone or in combination with internal electrostatic bonds (see below).
- *Internal H-bonds and dipole-dipole interactions:* These are the most important internal electrostatic bonds between uncharged groups.
- *Internal ionic bonds:* These may exist in zwitterions, the partitioning of which is as yet very poorly understood. In particular, we have come to feel that there is a need to distinguish between two major types of zwitterions, namely the more usual ammonium-carboxylates, and the more delocalized guanidinium (or amidinium)-enolates.
- *Hydrophilic folding:* This is defined as a conformational change by which a solute maximizes the number and strength of internal electrostatic bonds (mainly H-bonds) and thus partly masks some of its polar groups from the solvent. The drive for hydrophilic folding comes from a non-polar solvent, the solute hiding its polar groups

away from this non-polar solvent in order to become less polar and resemble that solvent.

- *Proximity effects between polar and non-polar groups:* This effect is detected as the decrease in their hydrophobic increment experienced of apolar moieties in the proximity of polar groups (i.e., lipophilicity is decreased). For example, 2,6-di-isopropyl phenol or aniline have have lower than expected log P values.

C) Steric/Hydrophobic Effects

- *Shielding of polar groups:* In some solutes, polar groups are shielded from the solvent by bulky hydrophobic moieties and are thus prevented from expressing their full polarity (i.e., lipophilicity is increased). This effect involves the same type of partner groups (polar and non-polar) as the proximity effect discussed just above, yet its effect on lipophilicity goes in the opposite direction. A subtle and poorly understood balance of intramolecular factors may be at work here, such that minute changes in relative contributions will lead to major changes in outcome (non-linear behavior) (17).
- *Hydrophobic interactions:* Alkyl or aryl moieties may form intramolecular hydrophobic interactions if this is compatible with their relative position and the compound's flexibility. As a rule, such internal hydrophobic interactions are characteristic of folded conformers, and render the solute less lipophilic than predicted by partly masking the hydrophobic moieties from the solvent (18).
- *Hydrophobic collapse:* This concept derives from the effect described in the previous section but conveys the idea of a phenomenon of particular magnitude (19,20). In other words, hydrophobic collapse as generally understood should be restricted to solutes of comparatively large molecular weight (several hundred or more) and containing a number of hydrophobic moieties able to come close together to create a hydrophobic core.

Structural Factors Influencing Intramolecular Interactions

In a schematic manner, the intramolecular interactions listed above depend on the following factors:

- The chemical and physicochemical nature of the moieties, e.g. their high or low polarity;
- Their distance from each other;
- The nature and number of interconnecting atoms.

In other words, a number of structural factors (geometric factors and molecular states) will influence intramolecular interactions and hence solubility and partitioning (Figure 2) (15):

A) Positional Isomerism. This geometric factor is of obvious significance in lipophilicity and may subdivided into:

- *Regioisomerism,* which relates positional isomers whose interconvertion is a *high-energy* process.
- *Tautomerism,* which involves the *low-energy* migration of a proton from one heteroatom to another.

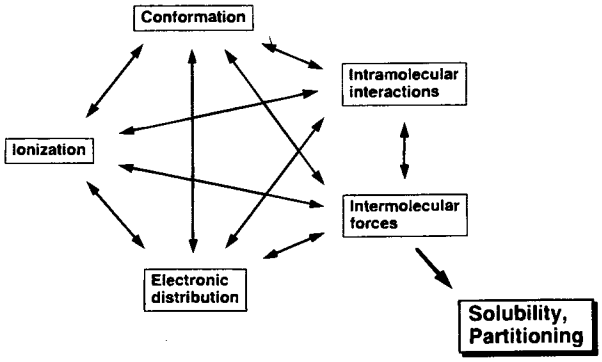


Fig. 2. Interrelated factors influencing intramolecular interactions, intermolecular forces and partitioning (15).

B) Stereoisomerism. This is another important geometric factor in lipophilicity. It is convenient to distinguish between:

- *Diastereomerism,* which relates diastereomers whose interconvertion is a *high-energy* process.
- *Conformational isomerism,* which involves the *low-energy* interconversion of stereoisomers.

C) Ionization. The possibility for a solute to exist in neutral or charged states will obviously have a major impact on its partitioning behavior. First, the solute will exhibit pH-dependent partitioning, making it indispensable to distinguish between its partition coefficients (solvent-dependent) and its distribution coefficients (pH- and solvent-dependent) (4). Second, the fact that a polar group exists in a neutral or charged state may dramatically alter the intramolecular interactions involving this group.

D) Molecular Size and Chameleonic Behavior. The phenomenon of self-coiling is a capital one not only for endogenous compounds, but also for drugs and other xenobiotics and their metabolites (21). Self-coiling, be it due to hydrophobic collapse or to hydrophilic folding, requires a certain number of structural conditions to be fulfilled, namely *functionalities, flexibility* and *size.* As a result of hydrophobic collapse and/or hydrophilic folding, a solute may become more polar in polar solvents and more lipophilic in lipidic solvents. In effect, such a solute to some extent adapts its lipophilicity to that of the medium, thereby behaving analogously to a *chameleon* which changes color to resemble that of the environment (22).

THE MOLECULAR LIPOPHILICITY POTENTIAL AND ITS VALIDATION

Calculation of the MLP

The molecular lipophilicity potential (MLP) is a transformation of the log $P_{octanol/water}$ value of a solute (conceptually a one-dimensional representation) into a three-dimensional representation. The MLP describes the combined lipophilic influence of all fragments of a compound on its molecular environment. Being a potential, it can be sampled (calculated) at given points in space. This calculation necessitates a fragmental system of

lipophilicity (23–26) and a distance function (6,7). The following equation is used (Eq. 4):

$$MLP_k = \sum_{i=1}^{N} f_i \cdot fct(d_{ik}) \qquad \text{(Eq. 4)}$$

where

k = index of a given point in space
i = index of a molecular fragment
N = total number of fragments in the molecule
f_i = lipophilic constant of fragment i
fct = distance fonction
d_{ik} = distance between fragment i and point k

In contrast to the electrostatic potential, the MLP is not revealed by using a probe. Rather, all interactions with the molecular environment are implicitely contained in the lipophilic fragmental values. The various MLP methods in the literature use different fragmental systems and different distance functions (12). They all do well in describing qualitatively the variations of lipophilicity in space, but little attention has been paid until now to the quantitative aspects of the MLP.

Validation of the MLP

We have based the quantitation and validation of the MLP on the hypothesis that, since it is a single number transformed into a three-dimensional representation, "back-calculation" from a finite region of space should yield the starting number if no information is lost when calculating the MLP (11). The solvent-accessible surface area (SAS) was chosen as the integration space since it simulates adequately the manner in which a compound is perceived by its environment (27,28). A simple numerical integration is performed with the sum of the MLP values calculated on the SAS covered with a fixed density of points.

Two parameters are used as independent variables in a multilinear regression where log $P_{octanol/water}$ is the dependent variable:

- The ΣMLP^+ parameter, i.e. the total of positive MLP values, represents the lipophilic part of the molecule.
- The ΣMLP^- parameter, i.e. the total of negative MLP values, represents the polar part of the molecule.

We have thus calculated the log $P_{octanol/water}$ values of 114 non-ionizable rigid solutes (mono- and disubstituted benzenes, protected amino acids, cyclodipeptides, etc) covering a range of values between −2.5 and +3.5. This approach has allowed us to select both the distance function and the lipophilic fragmental system giving the best agreement with experimental log P values.

Several distance functions were tested: the hyperbolic function defined by Dubost *et al.* (6), the exponential function used by Fauchère (7), and a modified exponential function (11) chosen to allow a strong attenuation of the MLP at a distance. Recently, a new distance function has been described by Brickmann *et al.* (10). This Fermi type function is controled by the two constants ***a*** and ***b***, the former defining the rate of decrease and the second the position of the inflection point. Using *para*-disubstituted benzenes, the constants ***a*** and ***b*** could be fixed at being equal to 1.33 and 3.25.

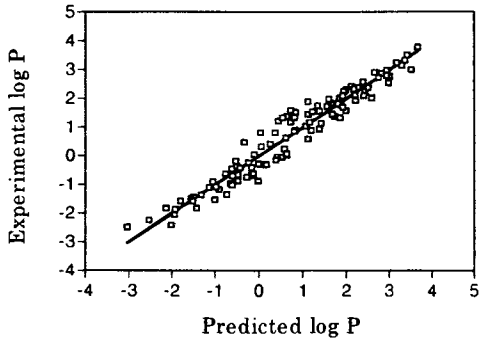


Fig. 3. Prediction of lipophilicity by integration of the MLP calculated with the atomic fragmental system of Broto *et al.* (23).

As a result, the MLP is currently calculated using a modified Eq. 4, namely equation 5:

$$MLP_k = \sum_{i=1}^{N} f_i \cdot \frac{1 + \exp(-ab)}{1 + \exp[a(d_{ik} - b)]} \qquad \text{(Eq. 5)}$$

where:

a = 2/Dd where Dd is the interval of half-decrease of the Fermi function
b = central point of the function

Two atomic fragmental systems were tested, those of Broto *et al.* (23) and of Ghose and Crippen (24,29). The correlation between experimental log P values and the integration parameters of the MLP is described equation 6 and Figure 3 for the fragmental system of Broto *et al.*, and by equation 7 and Figure 4 for the fragmental system of Ghose and Crippen.

$$\log P = 2.86 \cdot 10^{-3}(\pm 0.24 \cdot 10^{-3}) \sum MLP^+ + 1.52 \cdot 10^{-3}(\pm 0.22 \cdot 10^{-3}) \sum MLP^- - 0.10(\pm 0.23) \qquad \text{(Eq. 6)}$$

$$n = 114;\quad q^2 = 0.94;\quad r^2 = 0.94;\quad s = 0.37;\quad F = 926$$

$$\log P = 2.35 \cdot 10^{-3}(\pm 0.39 \cdot 10^{-3}) \sum MLP^+ + 1.78 \cdot 10^{-3}(\pm 0.50 \cdot 10^{-3}) \sum MLP^- - 0.39(\pm 0.39) \qquad \text{(Eq.7)}$$

$$n = 114;\quad q^2 = 0.88;\quad r^2 = 0.89;\quad s = 0.53;\quad F = 259$$

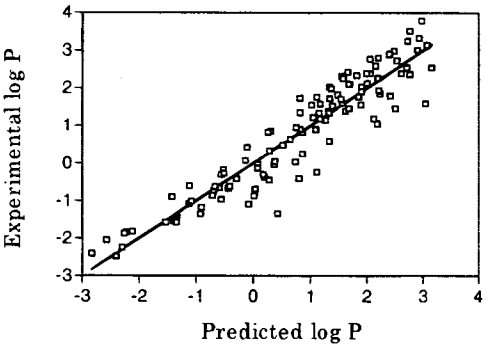


Fig. 4. Prediction of lipophilicity by integration of the MLP calculated with the atomic fragmental system of Ghose and Crippen (24,29).

These two models are of good statistical quality and demonstrate that the calculation of the MLP from fragmental constant indeed involves little loss of information. Equation 6 appears slightly better than equation 7, but no conclusion should be drawn from this preliminary observation. Interestingly, the explicit consideration of hydrogen atoms as done in the fragmental system of Ghose and Crippen does not improve the prediction of log P. In conclusion, integrating the MLP on the SAS allows a successful back-calculation of log P values in the explored range. The major limitation of this approach appears to be the precision of the atomic fragmental system used.

The solvent-accessible surface area (SAS) is highly dependent on the 3D-structure of the molecule. Due to this fact, the quantitative MLP affords a modeling tool allowing for the first time to calculate and visualize conformational effects on lipophilicity. In other words, the MLP open the door to studying lipophilicity variations in the conformational space of flexible compounds and to modeling their distribution profile (30).

CONFORMATIONAL EFFECTS ON LIPOPHILICITY: THE CHAMELEONIC BEHAVIOR

Background and Methods

The pharmacokinetic of flexible drug molecules is markedly influenced by their conformational behavior. As explained above, flexible compounds with suitable moities may exhibit hydrophobic collapse in polar solvents, and hydrophilic folding in lipidic environments (15, 31). These conformational changes are postulated to allow flexible compounds to adapt to and mimic their environment, and thus to distribute with greater ease between aqueous and lipidic compartments in the body.

To assess conformational effects on lipophilicity, it is essential to perform two operations. First, the conformational space of the solute under study must be investigated in a cost-effective manner. Among the various computational tools available to explore a conformational space (32), we have chosen high-temperature molecular dynamics. And second, the MLP of each retained conformer is calculated on its SAS and transformed into a *virtual log P* using equation 6.

The Lipophilicity Range of L-Dopa Esters

To illustrate the exploration of lipophilicity space, we present here the case of esters of L-Dopa. In an attempt to increase the systemic availability of L-Dopa used in the treatment of Parkinson's disease, aryl and alkyl esters of L-Dopa were prepared (33). Hydrolysis studies showed that the aryl esters underwent faster enzymatic hydrolysis than the alkyl esters, an effect that was not due to steric, electronic or lipophilic factors. The range of conformationally accessible log P values was then explored. The calculation of a virtual log P value for each conformer showed clearly that folded conformers are more polar than extended ones. This change in lipophilicity may be attributed to a decrease in the hydrophobic accessible surface in folded conformers as illustrated for the phenoxyethyl ester (Figure 5).

A comparison with experimental log P values revealed a different profile for the two classes of esters. The experimental partition coefficients were closer to the more polar virtual log P for alkyl esters and closer to the more lipophilic virtual log P for aryl esters. This difference suggests that the conformational behavior in solution could be different in the two series of esters, the alkyl esters existing largely as folded conformers whereas the aryl esters prefer extended conformations. These conformational changes affect the accessibility of the ester function and thus could be responsible, at least for a part, for the differences in rates of hydrolysis exhibited by alkyl and aryl esters.

CONCATENATION OF THE MLP IN CoMFA

Since it takes intermolecular recognition forces into account, the MLP should also be of value in the study of interactions between ligands and binding sites. Based on this hypothesis, we have demonstrated that the MLP can make a significant contribution to three-dimensional quantitative structure-activity relationships (3D-QSAR). We have also begun adapting the MLP into a docking tool in molecular modeling, as summarized in the next section.

Comparative Molecular Field Analysis (CoMFA) is currently a popular 3D-QSAR technique (34, 35). While its successes are innumerable, CoMFA also has some limitations, one of which is its reduction of ligand-receptor complexes to intermolecular interactions described only by two classic potentials, namely a steric molecular field quantified with a Lennard-Jones function, and an electrostatic field quantified by a Coulombic potential. It is obvious that these two molecular fields cannot take into account all the complex intermolecular forces between ligands and receptors. Another important limitation of the current CoMFA methodology is due to the fact that its two molecular fields are purely enthalpic and fail to take into account the entropic component of the free energy of binding (36).

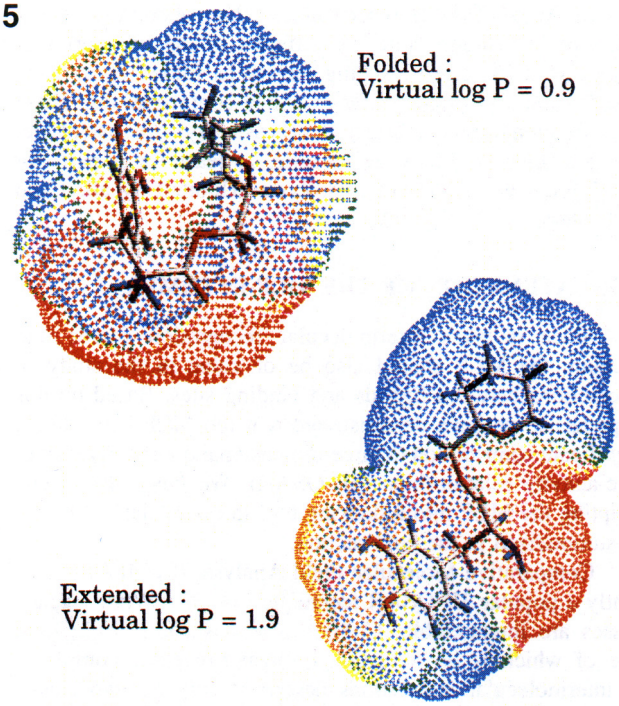
One approach to overcome these limitations is the introduction into CoMFA of a molecular field of lipophilicity which should enrich the modeling of ligand-receptor interactions. Since the MLP is derived from experimental partition coefficients, it describes implicitly the entropy component of the binding free energy associated with solvation/desolvation of the ligand and binding site.

A number of successful concatenations of the MLP into CoMFA have been published by our group or are in progress. They include structure-affinity relationships of a large series of 5-HT_{1A} receptor ligands (37), structure-activity relationships of indeno[1,2-c]pyridazines (38) and isoquinolines (39) as inhibitors of monoamines oxidases A and B, as well as the sweetening power of halogenated saccharose derivatives (40). In these examples, the MLP did improve the statistical quality of CoMFA models and their predictive capacity in test sets of compounds.

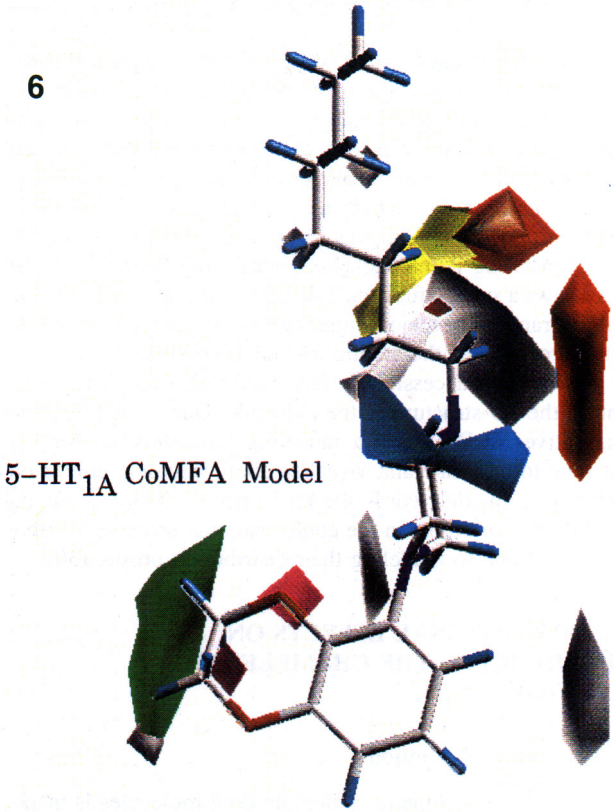
The benefits of the concatenation of MLP into CoMFA was illustrated by the final 3D-QSAR of the affinity of 5-HT_{1A} ligands (37) (Figure 6).

The steric and electrostatic signals near the aromatic part of the ligands (green, white and magenta regions) underline the importance of the *ortho* substitution by electron-withdrawing bulky groups for enhancing affinity whereas the large steric signal around the basic nitrogen (red region) is compatible with an ionic interaction between the receptor and ligands. All these signals are also present without the MLP field. However, by

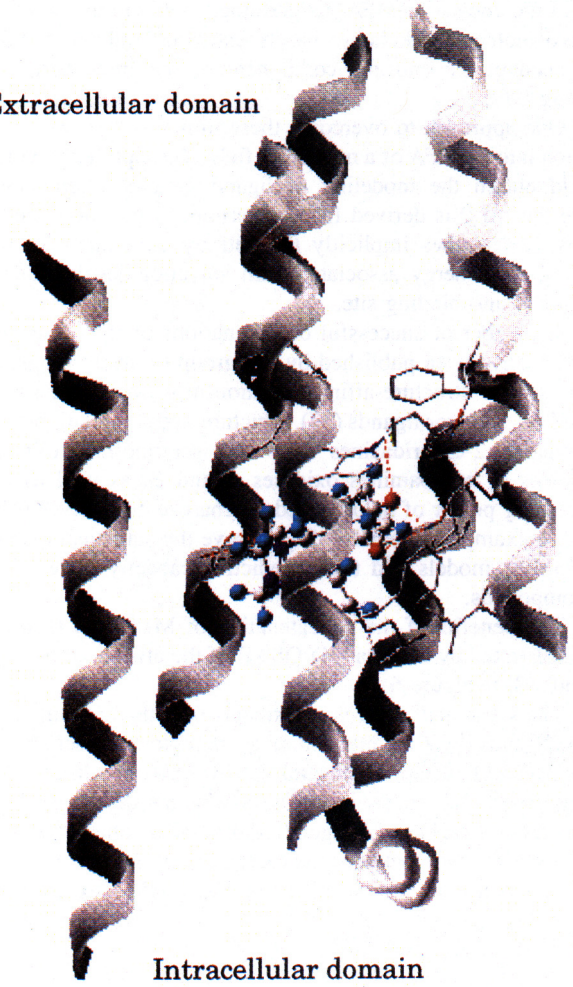
5


Folded :
Virtual log P = 0.9
Extended :
Virtual log P = 1.9
log P (exp) = 1.65

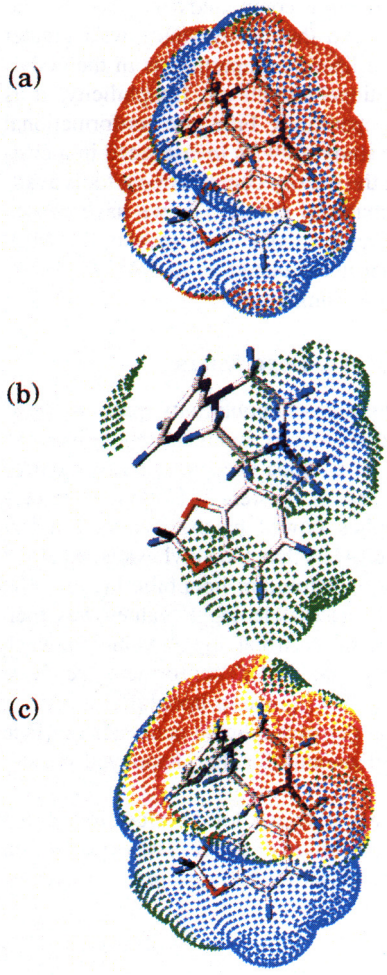
6


5–HT1A CoMFA Model

8


Extracellular domain
Intracellular domain

9


(a)
(b)
(c)

adding the MLP, a blue region appears near the secondary alcoholic group of aryloxypropanolamines suggesting an additional polar interaction of this group with the receptor. The existence of this blue region underlines that polar interactions are not always well-described by an electrostatic field only.

THE MLP AS A DOCKING TOOL

Since ligand binding is controlled by a number of intermolecular forces many of which are expressed in lipophilicity (see above), the most stable ligand-receptor complexes should be characterized by a maximal similarity between two MLPs, namely that generated by the ligand and that generated by the binding site.

Intrinsic MLP, Perceived MLP, and Similarities Between Them

Based on the above assumption, we have defined the van der Waals surface of the ligand as a working surface on which two MLPs are to be calculated. These are the *intrinsic MLP*, i.e. the MLP generated by the ligand on this surface, and the *perceived MLP*, i.e. the MLP generated by the binding site. To quantitate the similarity between the two MLPs, a similarity function has been defined (Eq. 8):

$$\text{Similarity} = \sum_{k=1}^{Nb_{dots}} (MLP_k)^{Int} \cdot (MLP_k)^{Per} \qquad \text{(Eq. 8)}$$

Thus, the more positive the score function, the greater the similarity between intrinsic and perceived MLP. In contrast, the greater the dissimilarity, the more negative the score function. At the time these pages were written, the similarity function was used to investigate the binding mode of the atypical D_2-agonist piribedil to the D_2 receptor.

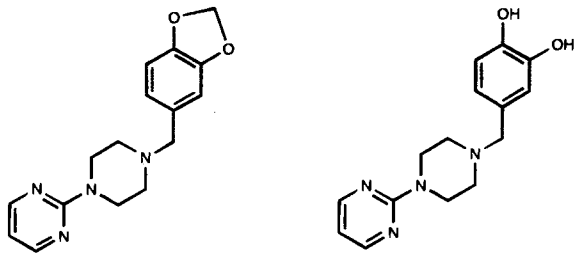
Example: Binding Modes of Some D_2 Receptor Agonists

1-(2-Pyrimidil)-4-piperonyl piperazine (Piribedil) (Figure 7) is a non-catechol analogue of dopamine of value in the treatment of affective disorders (41). This compound displays an affinity for the D_2 receptor which is higher (pK_i = 6.2) than that of its main metabolite (Figure 7) having a free catechol group (pK_i = 4.9) (42). In order to understand the origin of this unexpected behavior, several strategies were followed to dock piribedil and its main metabolite to the D_2 receptor model developped by Strange *et al.* (43). A number of interesting results were obtained for the most stable complexes involving piribedil (Figure 8) and its metabolite (not shown):

- To reinforce the ionic interaction between the basic amino group of the ligand and the carboxylic group of Asp114 in helix III, both piribedil and its metabolite should adopt a folded conformation leading to an enhanced accessibility of the basic nitrogen.
- Additional anchor points were found, namely π-π stacking or hydrophobic interactions with Trp 387 and Phe383 in helix VI, hydrophobic interactions with Ile158 in helix IV, and H-bonds with Ser194 and/or Ser197 in helix V.

On the base of interactions energies only, the relative importance of these intermolecular interactions was difficult to assess. However, the similarity function (Figure 9) suggests that the hydrophobic interactions of piribedil and its metabolite with the aromatic and aliphatic side-chains are more important than H-bonds for stabilizing the ligand-receptor complexes. The importance of hydrophobic interactions is also illustrated by the similarity function calculated for the binding mode of some rigid D_2-agonists (naxagolide and apomorphine) to the same D_2 receptor model (not shown).

Interestingly, the ranking of the MLP-based similarity function follows the relative order of binding energies of piribedil and its metabolite. Work is in progress to determine if a



Piribedil Piribedil metabolite, S584

Fig. 7. The structure of piribedil and its primary metabolite.

Fig. 5. Examples of extended and folded conformers of the phenoxy ethyl ester of L-DOPA. Due to an internal hydrophobic interaction, folded conformers are more polar (*virtual* log P = 0.9) than the extended conformers (*virtual* log P = 1.9). The MLP is displayed on the solvent-accessible molecular area. On all our MLP representations, the color coding follows a scale starting from the most polar regions to the most hydrophobic regions, namely red, orange, yellow, white, green, greenblue, blue.

Fig. 6. Graphical results of 3D-QSAR final model for 5-HT_{1A} affinity. N-(5-1,4-benzodioxan)-N′-octyl-piperazine is displayed and coloured by atom types. The red and green regions correspond to the steric field signal (prohibited and allowed for a bulky substituent), the gray and magenta regions correspond to the electrostatic signal (prohibited and allowed for a negatively charged substituent) and the yellow and blue regions correspond to the lipophilic signal (prohibited and allowed for a polar substituent) (37).

Fig. 8. Binding mode of piribedil in the D_2 receptor model. Piribedil is represented in ball and stick and the important side-chains of the receptor are colored by atom type. Only five transmembrane helices are displayed. Hydrogen bonds are colored in yellow.

Fig. 9. (a): Intrinsic MLP of piribedil in the bound geometry. For color coding, see Figure 5. (b): Similarity function between the intrinsic and perceived MLP of piribedil in its bound conformation. MLPs and similarity scores are displayed on the van der Waals surface of the molecule. The color coding for the score function follows a scale starting from the most dissimilar regions to the most similar regions with the following colors: red, orange, yellow, white, green, greenblue, blue. (c): Perceived MLP of piribedil in the bound geometry. For color coding, see Figure 5.

QSAR tool can be derived from the score function of stable ligand-receptor complexes.

CONCLUSION

Because the MLP is based on experimental data and provides an informative description of intermolecular recognition forces, it increases the versatility of computational tools in drug design. First, the MLP allows an exploration of the interconnectedness between the lipophilicity and three-dimensional topology of chemical compounds. Second, it affords an improved treatment of hydrophobic interactions and hydrogen bonds in 3D-QSAR when blended into CoMFA. The same is true when the MLP is used as a docking tool to investigate ligand-receptor interactions.

Various improvements of the MLP are desirable and feasible. Developing a better lipophilic fragmental system on which to base the MLP is one of the challenges. And developing other MLPs for solvent systems different from the octanol/water medium will create new possibilities.

ACKNOWLEDGMENTS

BT and PAC are indebted to the Swiss National Science Foundation for support.

REFERENCES

1. F. Helmer, K. Kiehs, and C. Hansch, The linear free-energy relation between partition coefficients and the binding, and conformational perturbation of macromolecules by small organic compounds. *Biochem.* **7**:2858–2863 (1968).
2. C. Hansch and A. Leo. *Substituent Constants for Correlation Analysis in Chemistry and Biology.* John Wiley and Sons, New York, 1979.
3. R. F. Rekker. *The Hydrophobic Fragmental Constant.* Elsevier, Amsterdam, 1977.
4. H. van de Waterbeemd and B. Testa. The parametrization of lipophilicity and other structural properties in drug design. In B. Testa (ed.), *Advances in Drug Research. Vol. 16,* Academic Press, London, 1987, pp. 87–227.
5. N. El Tayar, B. Testa, and P. A. Carrupt, Polar intermolecular interactions encoded in partition coefficients: an indirect estimation of hydrogen-bond parameters of polyfunctional solutes. *J. Phys. Chem.* **96**:1455–1459 (1992).
6. E. Audry, J. P. Dubost, J. C. Colleter, and P. Dallet, A new approach to structure-activity relations: the "molecular lipophilicity potential". *Eur. J. Med. Chem.* **21**:71–72 (1986).
7. J. L. Fauchère, P. Quarendon, and L. Kaetterer, Estimating and representing hydrophobicity potential. *J. Mol. Graphics* **6**:203–206 (1988).
8. P. Furet, A. Sele, and N. C. Cohen, 3D molecular lipophilicity potential profiles: a new tool in molecular modeling. *J. Mol. Graphics* **6**:182–189 (1988).
9. G. E. Kellogg, S. F. Semus, and D. J. Abraham, HINT: a new method of empirical hydrophobic field calculation for CoMFA. *J. Comput.-Aided Mol. Des.* **5**:545–552 (1991).
10. W. Heiden, G. Moeckel, and J. Brickmann, A new approach to analysis and display of local lipophilicity/hydrophilicity mapped on molecular surfaces. *J. Comput.-Aided Mol. Des.* **7**:503–514 (1993).
11. P. Gaillard, P. A. Carrupt, B. Testa, and A. Boudon, Molecular lipophilicity potential, a tool in 3D-QSAR. Method and applications. *J. Comput.-Aided Mol. Des.* **8**:83–96 (1994).
12. D. J. Abraham and G. E. Kellogg. Hydrophobic fields. In H. Kubinyi (ed.), *3D QSAR in Drug Design. Theory Methods and Applications.* ESCOM Science Publishers, Leiden, 1993, pp. 506–522.
13. R. W. Taft, J. L. M. Abboud, M. J. Kamlet, and M. H. Abraham, Linear solvation energy relations. *J. Sol. Chem.* **14**:153–186 (1985).
14. N. El Tayar, R. S. Tsai, B. Testa, P. A. Carrupt, and A. Leo, Partitioning of solutes in different solvent systems: the contribution of hydrogen-bonding capacity and polarity. *J. Pharm. Sci.* **80**:590–598 (1991).
15. B. Testa, P. A. Carrupt, P. Gaillard, and R. S. Tsai. Intramolecular interactions encoded in lipophilicity: their nature and significance. In V. Pliska, B. Testa, and H. van de Waterbeemd (eds.), *Lipophilicity in Drug Research,* VCH Publishers, Weinheim, 1996, in press.
16. R. F. Rekker and H. M. De Kort, The hydrophobic fragmental constant; an extension to a 1000 data point set. *Eur. J. Med. Chem.* **14**:479–488 (1979).
17. L. B. Kier and B. Testa. Complexity and emergence in drug research. In B. Testa and U.A. Meyer (eds.), *Advances in Drug Research. Vol. 26,* Academic Press, London, 1995, pp. 1–43.
18. C. Hansch and S. M. Anderson, The effect of intramolecular hydrophobic bonding on partition coefficient. *J. Org. Chem.* **32**:2583–2586 (1967).
19. R. A. Wiley and D. H. Rich, Peptidomimetics derived from natural products. *Med. Res. Rev.* **13**:327–384 (1993).
20. D. H. Rich. Effect of hydrophobic collapse on enzyme-inhibitor interactions. Implications for the design of peptidomimetics. In B. Testa, E. Kyburz, W. Fuhrer, and R. Giger (eds.), *Perspectives in Medicinal Chemistry,* VCH Verlag, Weinheim, 1993, pp. 15–25.
21. X. K. Jiang, Hydrophobic-lipophilicity interactions. Aggregation and self-coiling of organic molecules. *Acc. Chem. Res.* **21**:362–367 (1988).
22. P. A. Carrupt, B. Testa, A. Bechalany, N. El Tayar, P. Descas, and D. Perrissoud, Morphine 6-glucuronide and morphine 3-glucuronide as molecular chameleons with unexpected lipophilicity. *J. Med. Chem.* **34**:1272–1275 (1991).
23. P. Broto, G. Moreau, and C. Vandycke, Molecular structure: perception, autocorrelation descriptor and SAR studies. Perception of molecules: topological structure and 3-dimensional structure. *Eur. J. Med. Chem.* **19**:61–65 (1984).
24. A. K. Ghose and G. M. Crippen, Atomic physicochemical parameters for three-dimensional structure-directed quantitative structure-activity relationships. 1. Partition coefficients as a measure of hydrophobicity. *J. Comput. Chem.* **7**:565–577 (1986).
25. A. Kantola, H. O. Villar, and G. H. Loew, Atom based parametrization for a conformationally dependent hydrophobic index. *J. Comput. Chem.* **12**:681–689 (1991).
26. G. Klopman and S. Wang, A computer automated structure evaluation (CASE). Approach to calculation of partition coefficients. *J. Comput. Chem.* **12**:1025–1032 (1991).
27. P. Camilleri, S. A. Watts, and J. A. Boraston, A surface area approach to determination of partition coefficients. *J. Chem. Soc., Perkin Trans. 2* 1699–1707 (1988).
28. S. Hirono, Q. Liu, and I. Moriguchi, High correlation between hydrophobic free energy and molecular surface area characterized by electrostatic potential. *Chem. Pharm. Bull.* **39**:3106–3109 (1991).
29. A. K. Ghose and G. M. Crippen, Atomic physicochemical parameters for three-dimensional-structure-directed quantitative structure-activity relationships. 2. Modeling dispersive and hydrophobic interactions. *J. Chem. Inf. Comput. Sci.* **27**:21–35 (1987).
30. P. Gaillard, P. A. Carrupt, and B. Testa, The conformation-dependent lipophilicity of morphine glucuronides as calculated from their molecular lipophilicity potential. *Bioorg. Med. Chem. Lett.* **4**:737–742 (1994).
31. P. A. Carrupt, P. Gaillard, F. Billois, P. Weber, B. Testa, C. Meyer, and S. Pérez. The molecular lipophilicity potential (MLP) a new tool for log P calculation and in comparative molecular field analysis (CoMFA). In V. Pliska, B. Testa, and H. van de Waterbeemd (eds.), *Lipophilicity in Drug Research,* VCH Publishers, Weinheim, 1996, in press.

32. A. R. Leach. A survey of methods for searching the conformational space of small and medium-sized molecules. In K. B. Lipkowitz and D. B. Boyd (eds.), *Reviews in Computational Chemistry, Vol. II,* VCH, New York, 1991, pp. 1–55.
33. M. Brunner-Guenat, P. A. Carrupt, G. Lisa, B. Testa, S. Rose, K. Thomas, P. Jenner, and P. Ventura, Esters of L-Dopa: structure-hydrolysis relationships and ability to induce circling behaviour in an experimental model of hemiparkinsonism. *J. Pharm. Pharmacol.* **47**:861–869 (1995).
34. R. D. Cramer III, D. E. Patterson, and J. D. Bunce, Comparative molecular field analysis (CoMFA). 1. Effect of shape on binding of steroids to carrier proteins. *J. Am. Chem. Soc.* **110**:5959–5967 (1988).
35. R. D. Cramer III, S. A. DePriest, D. E. Patterson, and P. Hecht. The developing practice of comparative molecular field analysis. In H. Kubinyi (ed.), *3D QSAR in Drug Design. Theory Methods and Applications.* ESCOM Science Publishers, Leiden, 1993, pp. 443–485.
36. G. Klebe and U. Abraham, On the prediction of binding properties of drug molecules by comparative molecular field analysis. *J. Med. Chem.* **36**:70–80 (1993).
37. P. Gaillard, P. A. Carrupt, B. Testa, and P. Schambel, Binding of arylpiperazines, (aryloxy)propanolamines and tetrahydropyridyl-indoles to the 5-HT_{1A} receptor: contribution of the molecular lipophilicity potential to three-dimensional quantitative structure-activity relationship models. *J. Med. Chem.* **39**:126–134 (1996).
38. S. Kneubühler, U. Thull, C. Altomare, V. Carta, P. Gaillard, P. A. Carrupt, A. Carotti, and B. Testa, Inhibition of monoamine oxidase-B by 5H-indeno[1,2-c]pyridazine derivatives: biological activities, quantitative structure-activity relationships (QSARs) and 3D-QSARs. *J. Med. Chem.* **38**:3874–3883 (1995).
39. U. Thull, S. Kneubühler, P. Gaillard, P. A. Carrupt, B. Testa, C. Altomare, A. Carotti, P. Jenner, and K. S. P. McNaught, Inhibition of monoamine oxidase by isoquinoline derivatives: qualitative and 3D-quantitative structure-activity relationships. *Biochem. Pharmacol.* **50**:869–877 (1995).
40. C. Meyer. *Bases moléculaires du goût sucré: flexibilité conformationnelle et relations structure-activité d'édulcorants intenses dérivés du saccharose.* Université de Nantes, Nantes, 1994.
41. C. T. Dourish, Piribedil: behavioural neurochemical and clinical profile of a dopamine agonist. *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.* **7**:3–27 (1983).
42. Y. Evrard, Le piribédil, agoniste dopaminergique. *Actual. Chim. Thér.* **N° Spécial:** 16–20 (1991).
43. C. D. Livingstone, P. G. Strange, and L. H. Naylor, Molecular modelling of D_2-like dopamine receptors. *Biochem. J.* **287**:277–282 (1992).