Lipophilicity force field profile: An expressive visualization of the lipophilicity molecular potential gradient

F. Croizet,* M. H. Langlois,* J. P. Dubost,* P. Braquet,† E. Audry,* Ph. Dallet,* and J. C. Colleter*

**Groupe d'Etude des Relations Structure-Activité et d'Analyse Chimique, Laboratoire de Chimie Analytique U.R.A. 605, Bordeaux, France; and †Institut Henri Beaufour, Le Plessis Robinson, France*

This paper proposes a new tool that allows us to see the following in the same frame: (1) 3D geometrical features of a molecule, and (2) pseudo-3D representation of the lipohilicity molecular potential. It thus becomes very easy to compare the lipohilicity molecular potential gradient of different molecules having the same pharmacological properties. An example of two structurally dissimilar anti-PAF molecules is given.

Keywords: lipophilicity, lipophilicity molecular potential, QSAR

It is now accepted that lipophilicity is an important molecular property in the search for relationships between the chemical structure of a molecule and its biological activity.[1]

Log P, the partition coefficient, usually describes this property and is widely used for classical quantitative structure activity relationships (QSAR). However, this one-dimensional representation becomes insufficient when stereochemical features of molecules are analyzed in the context of intermolecular interactions with the receptor. To avoid this failure, we have recently introduced the notion of *molecular lipophilic potential*,[2,3] which takes into consideration that lipophilicity is a property distributed over all the different parts of a molecule. Lipophilic and hydrophilic regions in the surrounding space of a molecule are revealed by this concept.[4,5] So it is easier to compare different drugs even if they do not have the same framework.

Address reprint requests to Dr. Dubost at the Groupe d'Etude des Relations Structure-Activité et d'Analyse Chimique, Laboratoire de Chimie Analytique U.R.A., 605 Place de la Victoire, 33076 Bordeaux Cedex, France.
Received 5 December 1989; accepted 9 January 1990

THE MOLECULAR LIPOPHILICITY POTENTIAL

If a molecule is considered to be the sum of n independent fragments, the logarithmic partition coefficient value can be broken down into a sum of hydrophobic fragmental constants f_i [6]:

$$\log P = \sum_{i=1}^{n} f_i \tag{1}$$

where f_i is the lipophilic contribution of a constituent fragment of a molecule to the total lipophilicity.

For us, a fragment is a nonhydrogen atom connected with zero, one, two, or three hydrogen atoms. We have used f_i values published by Broto in the *European Journal of Medicinal Chemistry*.[7]

Let us consider a molecule, S, in an organic phase composed of nonpolar or slightly polar molecules, L. L molecules are distributed at random when they are far from S. This arrangement must be modified as the distance decreases. A lipophilic fragment (f_i positive) will tend to attract the L molecules, and a hydrophilic fragment (f_i negative) will tend to repulse L molecules.

We have defined at each point M in the space surrounding the S molecule a parameter called molecular lipophilicity potential (MLP):

$$\mathrm{MLP} = \frac{\sum_{i=1}^{n} f_i}{1 + d_i} \tag{2}$$

where d_i is the distance (Å) between the fragment i and the point M.

If $n = 1$, then equation 2 becomes

$$\mathrm{MLP} = \frac{f_i}{1 + d_i} \tag{3}$$

This is the lipophilicity potential generated by a fragment i on one point located at d_i. At d_i, MLP can be considered to be the fraction of the maximal affinity of the fragment to a receptor. Theoretically the MLP value varies, according to the molecule, from $-\infty$ to $+\infty$. So, to compare the lipophilic force field of different compounds with the same positive scale we used instead of the MLP value the PL probability function connected to the MLP by the following equation:

$$PL = \frac{10^{MLP}}{1 + 10^{MLP}} \quad (4)$$

As we have shown,[3] the value of PL in any point of the space surrounding a molecule placed in a solvent of low polarity represents the probability that a lipophilic solvent molecule exists at this very point. So we obtained a positive scale varying from 0 to 1 or from 0 to 100 if PL is expressed as a percentage.

LIPOPHILIC MOLECULAR FIELD PROFILE

Equation 4 quantifies the lipophilic properties of a molecule by the *lipophilic force field* that it creates in its surrounding area.

Classically, PL can be visualized by using a 2D isolipophilicity map[2] or color-coded isolipophilicity lines drawn on a molecular envelope.[8] But, whatever the representation, the gradient of the lipophilicity molecular potential is not very expressive. To avoid this failure we try in this work to visualize in the same frame, for a definite plane, the *profile gradient* of the lipophilic field of a molecule and the 3D geometrical compound of this compound.

To do that, the VISGRALIP program transforms the spatial coordinates of the molecule X, Y, Z into screen coordinates Xs and Ys according to the following equations:

$$Xs = Y - X \sin(30°)$$

$$Ys = X \cos(30°) - Z$$

For PL representation we assume that PL plays the role of the Z coordinate so X, Y, PL *spatial coordinates* are transformed into Xs and Ys screen coordinates by the relations

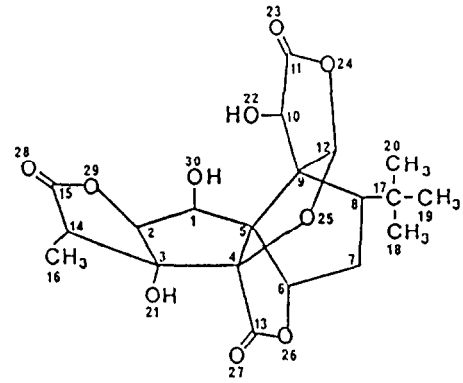
$$Xs = Y - X \sin(30°)$$

$$Ys = X \cos(30°) - PL$$

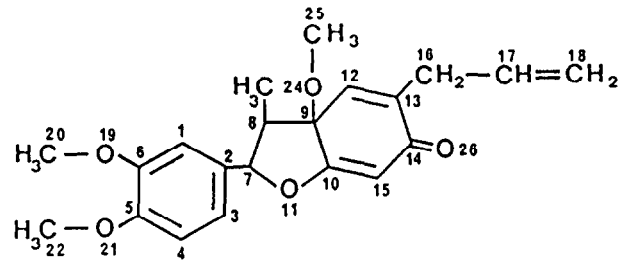
The superposition of these two projections leads to a pseudo-3D visualization of the lipophilic force field of a molecule.

AN EXAMPLE: COMPARISON OF LIPOPHILICITY FORCE FIELD OF A NATURAL PAF ANTAGONIST (BN 52022 (GINKGOLIDE B)) WITH A SYNTHETIC (KADSURENONE)

Platelet-activating factor (PAF) is a phospholipid mediator formed by different cells, such as eosinophilis, macrophages, platelets, neutrophils, and vascular endothelium. Because they play an important role in allergic and inflammatory reactions, different antagonists have been tested. Among these, ginkgolide B (natural product) and kadsurenone (synthetic product) are the more potent.[9]



BN 52021
GINKGOLIDE B



KADSURENONE

Figure 1. The two anti-PAF molecules

When we look at the chemical structure (Figure 1), the similarity between the two antagonists is not obvious. But when we observe the lipophilicity force fields (Color Plate 1), we notice that these two molecules present a lipophilic zone and an hydrophilic zone separated by approximately the same distance. So it seems reasonable to assume the following:

1. On one hand, the dimethoxy phenyl ring of the kadsurenone plays the role of the *tert*-butyl group of the ginkgolide B since each group generates a lipophilic zone.
2. On the other hand, the $C_{14}=O_{26}$ carbonyl group of the kadsurenone plays the role of carbonyl $C_{15}=O_{28}$ of ginkgolide B since they both generate the hydrophilic zone.

CONCLUSION

The example presented here shows that lipophilicity force field profile gives an expressive illustration of the molecular lipohilic potential gradient. With this method, it is easy to compare the lipophilicity of two different molecules. Because this tool needs only 3D atom coordinates and their f_i values it is easy to use and can work even without an expansive computer, such as a PC.

REFERENCES

1. Van de Waterbeemd, H., and Testa, B. The parametrization of lipophilicity and other structural properties in drug design. In *Advances in Drug Research,* Vol. 16. Academic, New York, 1987, pp. 87–225

2. Audry, E., Th. Etat Es Sc. Pharm., Bordeaux, 1985
3. Audry, E., Dubost, J. P., Colleter, J. C., and Dallet, Ph. Une nouvelle approche des relations structure-activité le "Potentiel de Lipophilie Moléculaire." *Eur. J. Med. Chem.–Chim. Ther.* 1986, 71–72
4. Audry, E., Dubost, J. P., Dallet, Ph., Langlois, M. H., and Colleter, J. C. Le Potentiel de Lipophilie moléculaire: Application à une série d'amines β-adrénolytique. *Eur. J. Med. Chem.–Chim. Ther.* 1989, 155–161
5. Dubost, J. P., Audry, E., Dallet, Ph., Montagut, M., and Carpy, A. Indirect molecular modelling approaches in the alpha adrenergic field. In *Q.S.A.R. in Drug Design and Toxicology,* Vol. 17. Elsevier Science, New York, 1987, pp. 169–172.2
6. Rekker, R. F. *The Hydrophobic Fragmental Constant.* Elsevier, Amsterdam, 1977
7. Broto, P., Moreau, G., and Vandycke, C. Molecular structures, perception, autocorrelation descriptor and SAR studies. *Eur. J. Med. Chem.–Chim. Ther.* 1984, **19**(1), 71–78
8. Furet, P., Sele, A., and Cohen, N. C. *J. Mol. Graphics,* 1988, **6**, 182–189
9. Braquet, P., Chabrier, P. E., Mencia-Huerta, J. M. In *Advances in Inflammation Research,* Vol. 12. Raven Press, New York, 1988, pp. 135–157