The computer program MolPot: a useful tool in chemical reactivity analysis

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MolPot is a fast program for producing reactivity diagrams of molecular compounds, particularly for drugs. These diagrams are characteristic of the molecule envelope and the Molecular Electrostatic Potential (MEP) of the molecule surface (van der Waals surface or the portion of this surface that is solvent accessible). The input data includes only the atom names and their Cartesian coordinates.

Keyword: Molecular Electrostatic Potential (MEP)

INTRODUCTION

Molecular Electrostatic Potential (MEP) has become a useful tool for analyzing chemical reactivity, especially after the quantum chemical studies of Scrocco and Tomasi (1978)[1] and Politzer and Truhlar (1981).[2] The recognition step can be described in terms of a fixed-nuclei model and is essentially determined by two factors: the molecular surfaces and their electrostatic potentials. These entities must form complementary pairs if their interaction is to lead to the formation of a stable or a metastable complex. The molecular envelope can be determined easily from the van der Waals radii of peripheral atoms.

In the case of drug-receptor interaction, the geometry of the receptor active site is rarely known. To determine the characteristic parameters of the receptor, the geometry of the interacting conformation of the drug molecule must be defined. Its characteristics in terms of molecular envelope and MEP will give the complementary image of the receptor active site.

The electrostatic potential can be determined using the fixed-nuclei MEP model. The potential from the field of the electron distribution (associated with a given quantum electronic state) and of the nuclei of a molecule on a point space defined by the radius vector $\mathbf{r}$, with respect to a given origin, is:

$$V(r) = \sum_A (Z_A/|\mathbf{R}_A - \mathbf{r}|) - \int \rho(\mathbf{r}')d\mathbf{r}'/|\mathbf{r}' - \mathbf{r}| \qquad (1)$$

Z_A is the charge of nucleus A and $\rho(\mathbf{r}')$ is the electron electronic density function density for the given electronic state. Note that the MEP depends on the geometry of a given molecule as well as on its electronic state.

The interaction between a molecule and other systems (e.g., molecule–ion) is the combination of several effects: electrostatic, dispersion, polarization and charge transfer. The corresponding energy is cumbersome to compute and can be calculated only for small systems. The electrostatic energy represents a major contribution to the perturbation energy and is the product of the MEP and the atomic charges; therefore, MEP is representative of the molecular reactivity. The MEP can be modeled in different ways. Equation 1 is a general expression that is difficult to evaluate exactly, especially in the case of macromolecules, so for simplicity we compute the MEP using the monopole approximation

$$V(r) = \sum_A q_A/(|\mathbf{R}_A - \mathbf{r}|) \qquad (2)$$

where q_A is the point charge located at $\mathbf{R}_A$.

If the potential V and the point $\mathbf{R}_A$ are given, it is always possible to determine a set of q_A's that satisfy equation 2 as accurately as possible. With most semiempirical methods of quantum chemistry, the approximation (Eq. 2) must be used in the right–left direction, and suitable and optimal charges must be known in order to determine the MEP in a monopole approximation.

Charge calculation: the procedure for empirically calculating net atomic charges consists of adding π charges and formal charges to σ charges in the same way as given by Langlet *et al.* (1981).[3]

The σ charges are computed with del Re's method[4] with a new set of atomic parameters.[5] The π charges are calculated in an empirical approximation in order to obtain Pariser and Parr[6] values. These charges are analogous to charges derived from *ab initio* MEP calculations,[5] with the advantage that even large molecules can be computed quickly using microcomputers.

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In our calculations the significant MEP values are those associated with the van der Waals envelope of the molecule. This corresponds to the assumption that nonelectrostatic forces (van der Waals) are of such a short range that they become negligible zero outside the van der Waals envelope. Under this assumption, a foreign ion or molecule A cannot penetrate a substrate M beyond the envelope, and therefore the interactions are essentially electrostatic. The above considerations assume that nonelectrostatic forces are well represented by the hard sphere model. This assumption is admittedly rather crude, but it is known to lead to reliable predictions for sterically hindered molecules. A serious objection could be that it does not allow for chemical bond formation. However, these objections do not apply since the bond formation and bond cleavage steps of reaction processes involve distances smaller than the van der Waals radii. Thus, they correspond to sections of the reaction path that must be described in terms of reactivity indices other than MEPs.

We also consider the van der Waals surface to be accessible to the solvent,[7] in order to remove unhelpful surface portions.

THE PROGRAM MolPot

Description of the surfaces

This program was written to draw characteristic diagrams of a molecule. Because the MEP is related to the molecular conformation, one diagram expresses the molecular conformation and the other one characterizes the reactivity.

Principles of calculations

The program offers three possibilities for orienting the molecule:

(1) The molecule can be kept in its initial orientation.
(2) A reference system can be defined by the user on three atoms belonging to the molecule; if they are not given, the program will take the three first nonhydrogen atoms.
(3) A reference system can be established on the molecule shape by the program as follows: The x-axis is defined by two atoms located in the largest dimension of the molecule, then the y-axis is defined by the atom the farthest from this axis.

The program determines the limits of the molecule along the z-axis and starts to cut parallel slices one angstrom thick, perpendicularly to this axis. The points of the envelope are determined as follows.

Once the centroid of the atoms (belonging to the slice) is determined, a vector centered on this point, with a modulus corresponding to the farthest atom of z-axis belonging to the slice, is used to perform a scan (Figure 1) of the slice. The edge corresponds to the intersection of this vector with the van der Waals surface of the atoms of the slice. The angular increment varies from one to three degrees and is inversely proportional to the distance of the centroid to the border. The starting point corresponds to the direction of the x-axis: The scanning is performed counterclockwise. In the case of the van der Waals surface accessible to the solvent, a sphere 1.4 Å in diameter is rolled on the surface previously defined. The new surface is defined by the contact points of this sphere with the van der Waals surface (see Figure 1) where a slice corresponding to the accessible van der Waals surface is represented. The dashed line is the MEP curve, and the section contour is taken as the zero potential line. ΔR is proportional to the potential, directed inward for a negative V and outward for a positive V.

The MEP is computed on all the surface points as described above.

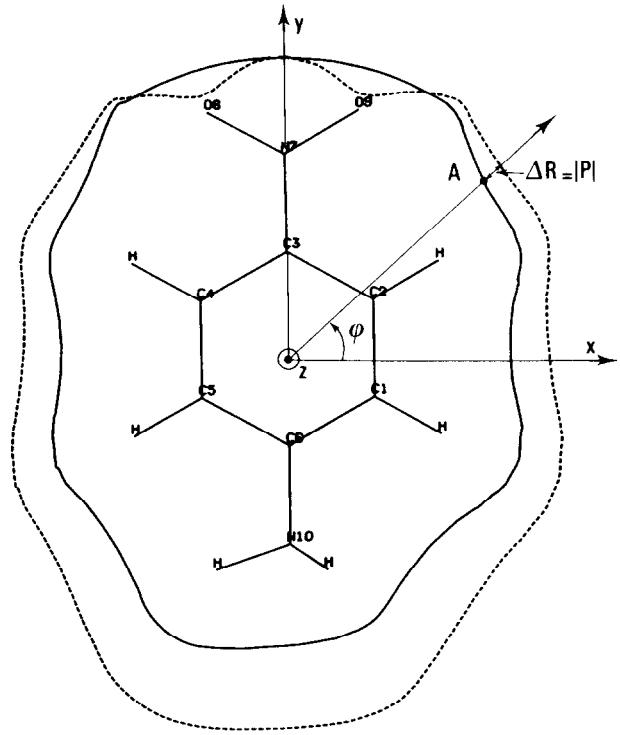

Figure 1. Representation of the MEP on a molecule slice of van der Waals surface that is accessible to the solvent. The dashed line is a radial representation of the MEP. ΔR is proportional to the MEP at point A. The section contour is the zero potential line

Characteristic diagrams of a molecule

In Figure 2a, the diagrams of the neurotransmitter noradrenaline are represented (the geometry used is from X-ray structure 8). In the right-hand part, the slices corresponding to the van der Waals surface are shown. The left diagram characterizes the molecular conformation with the area of each slice plotted in terms of the slice numbers (the van der Waals volume is the value of the integral of this curve). The molecule corresponding to the orientation of the given system of reference is drawn above the left diagram.

The right-hand diagram is characteristic of the reactivity. Each curve bears the number of its slice. The abscissa corresponds to the scanning angle. On the right vertical line, the numbers give the potential origin line for each slice, and the left-hand vertical line indicates the potential value in volts. Under this diagram the extreme values of the MEP and their positions on the corresponding slice are reported.

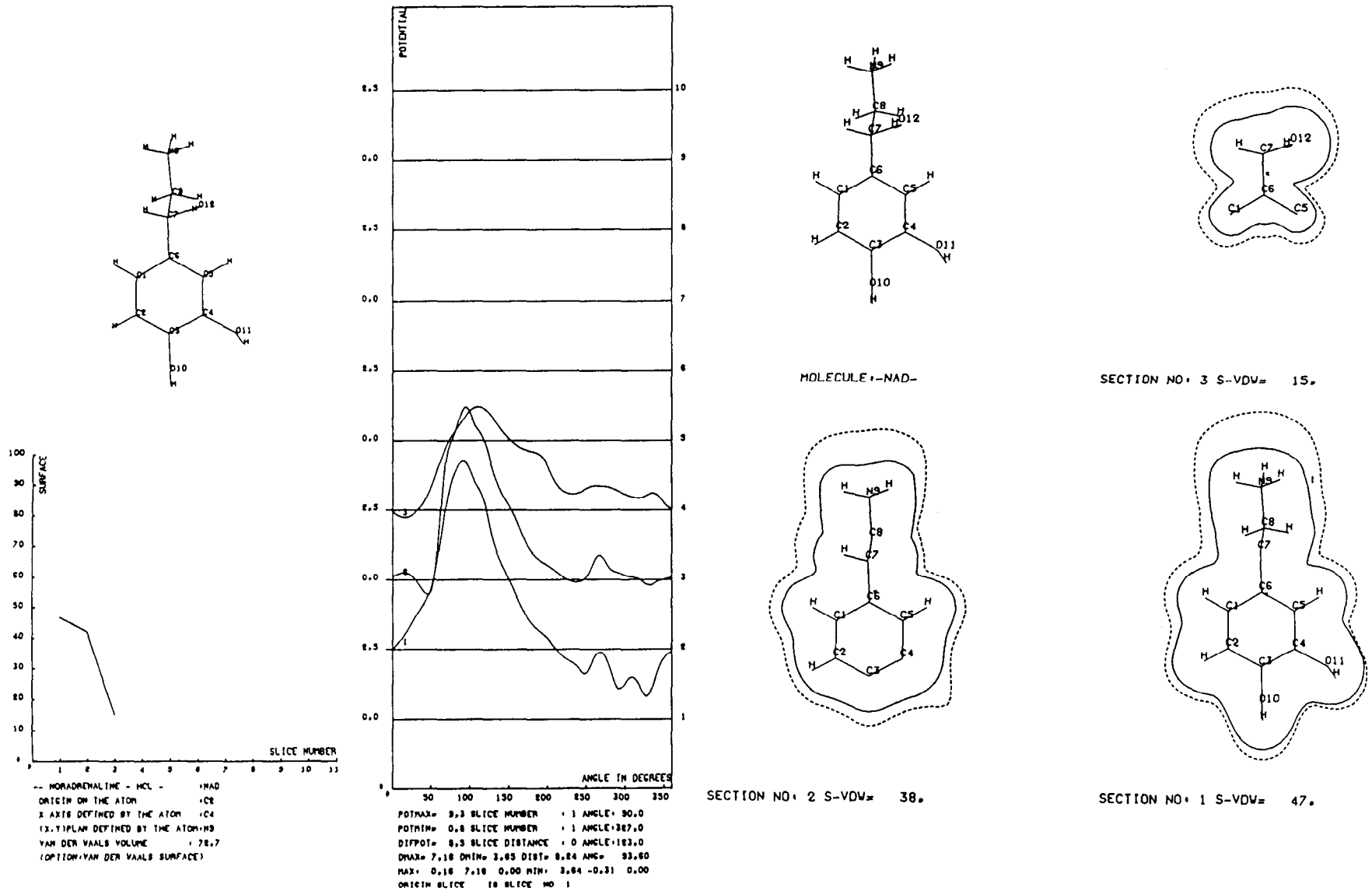

Figure 2a. Diagrams of noradrenaline characteristic of the van der Waals envelope: The right part represents the van der Waals slices perpendicular to z-axis of the Cartesian system as defined on the left part. The left diagram is characteristic of the molecular conformation. The surface area of each slice is plotted in terms of the slice number. The molecule drawing, above this diagram, is the Z projection. The MEP diagram is a representation of the MEP (in volts) along the slice contour. The numbers on the curves correspond to the slice numbers. The numbers on the right vertical line give the potential origin line for each slice

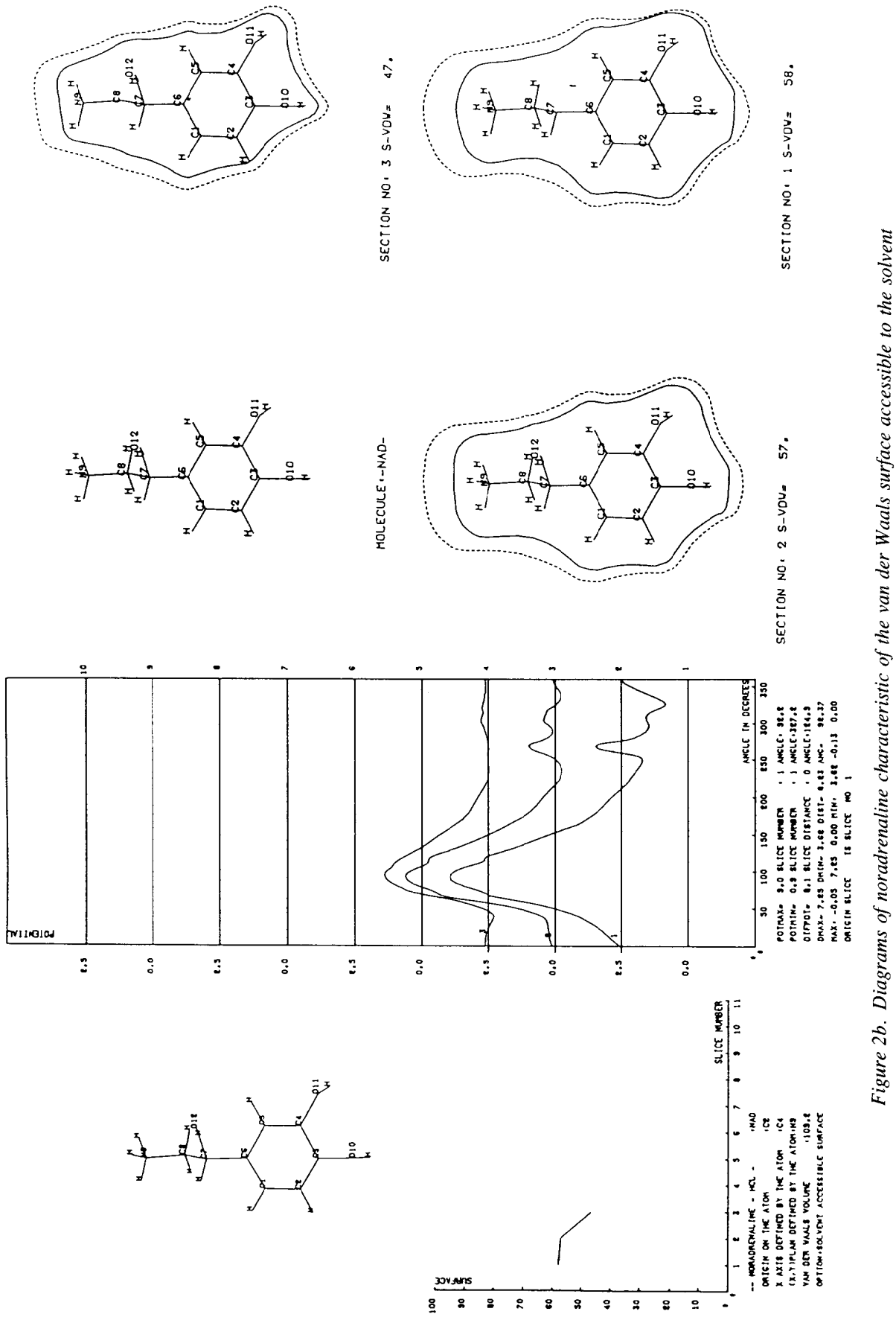

Figure 2b. Diagrams of noradrenaline characteristic of the van der Waals surface accessible to the solvent

DMAX and DMIN are, respectively, the distances of the MEP extreme values to the molecule centroid; DIST and ANG are, respectively, the distance between these points and the angle between the directions of these extrema. These last three values do not depend on the reference system. The positions of the extreme MEP values are also given in the Cartesian system established on the molecule. These positions are useful for performing comparisons on molecules or molecular conformations. The slice passing through the molecule centroid is the origin slice.

Figure 2b, corresponding to the solvent-accessible surface, emphasizes the differences between the van der Waals surface (Figure 2a) and that surface.

APPLICATIONS

In previous works that allow the prediction of neuroleptic or antidepressant activity of new tricyclic compounds,[9,10] interesting applications of the program are given.

In Figure 3a and Figure 3b the characteristic diagrams of the two conformations observed in the crystalline state[11] of an antidepressant drug (imipramine) are displayed. The orientation of the conformations is computed in option 3 (p. 234) of the program described above, and the diagrams correspond to the solvent-accessible surface. From these diagrams, we can predict substantial reactivity differences of these two conformations. The corresponding shapes are not

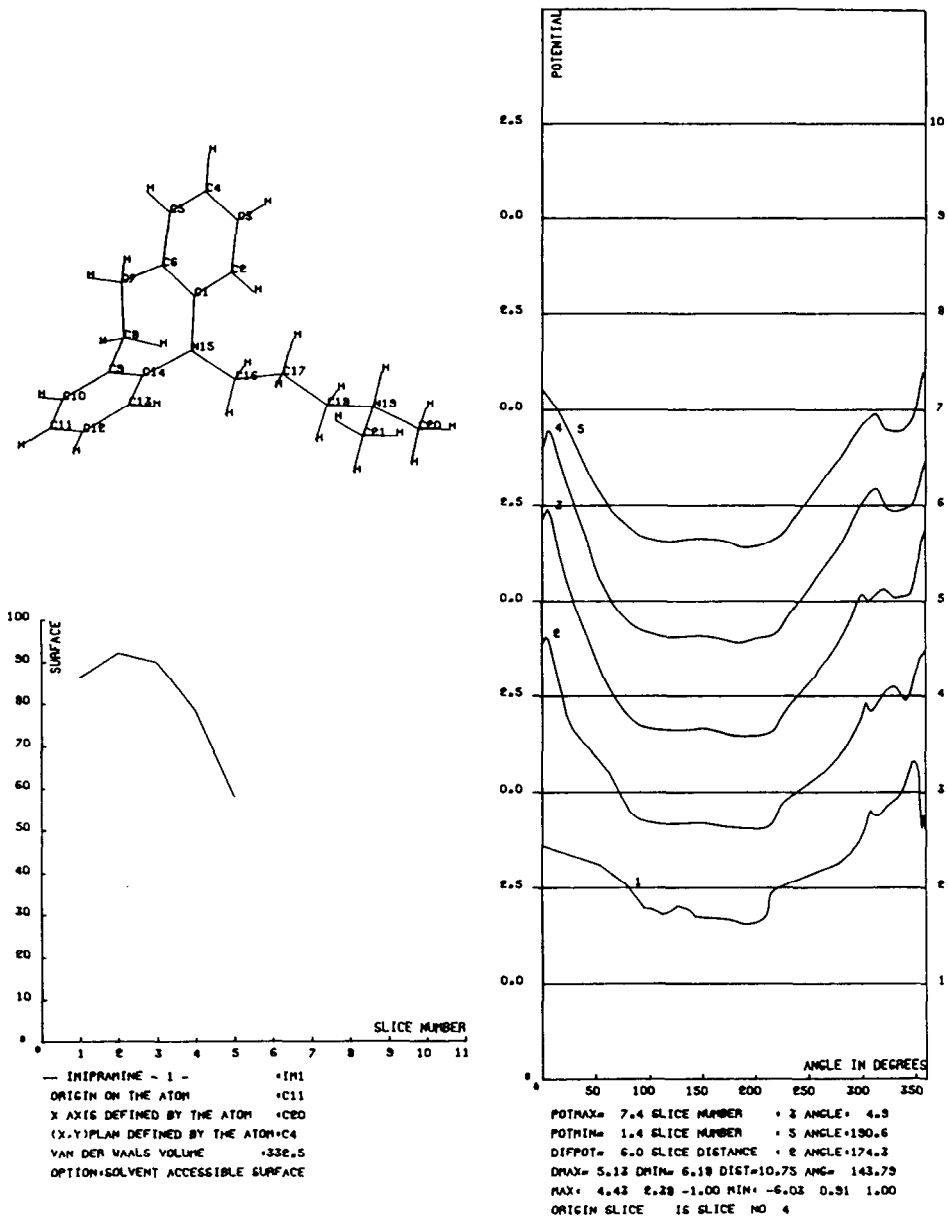

Figure 3a. Diagrams of conformation 1 of an antidepressant drug (imipramine) issued from X-ray analysis. They are characteristic of the van der Waals surface accessible to the solvent

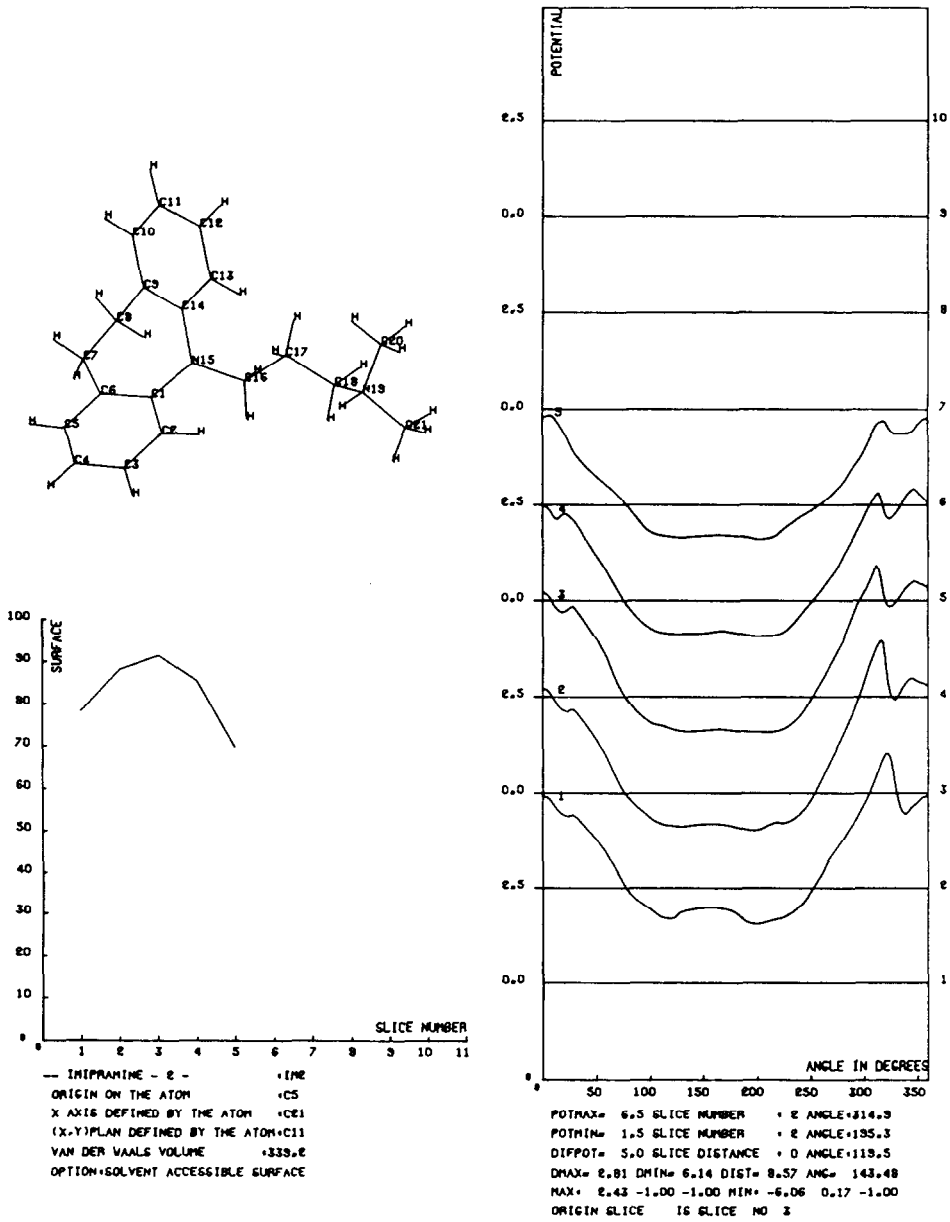

Figure 3b. Diagrams of conformation 2. The differences with Figure 3a can be correlated to differences of activity. From MEP values, conformation 1 is expected to be more active

similar, and the extreme MEP position and values are different (the MEP maximum value is 7.4 V for the conformation 1 instead of 6.5 V for conformation 2). It has been shown[9] that these differences probably lead the two conformations to interact with two different receptor families (presynaptic receptors of noradrenaline or of serotonine).

Comparing the active conformation diagrams of compounds belonging to the same drug family to their therapeutic activity establishes a relationship between molecule parameters and the activity. The drug molecules can then be modified in order to improve the therapeutic property.

TECHNICAL INFORMATION ON MolPot

MolPot[12] is a very fast program to compute MEP (a few seconds on a DEC MicroVAX II computer for a 50-atom molecule). It is a 3000-line program written in FORTRAN 77. The input data includes only the atom names and their Cartesian coordinates. It is not computer dependent and needs a graphics terminal or a plotter.

REFERENCES

1 Scrocco, E. and Tomasi, J. *Adv. Quant. Chem.* 1978, **11,** 115

2 Politzer, P. and Truhlar, D.G., Eds. *Chemical Application of Atomic or Molecular Electrostatic Potentials.* New York: Plenum Press, 1981

3 Langlet, J., Claverie, P., Caron, F. and Boeve, J.C. *Int. J. Quant. Chem.* 1981, **19,** 299

4 Del Re, G. *J. Chem. Soc.* 1958, **40,** 31

5 Pèpe, G., Serres, B., Laporte, D., Del Re, G. and Minichino, C. *J. Theor. Biol.* 1985, **115,** 571
6 Pariser, P. and Parr, R.G. *J. Chem. Phys.* 1953, **21,** 446, 767
7 Connolly, M.C. *Science* 1983, **221,** 709
8 Carlstroem, D. and Bergin, R. *Acta Cryst.* 1967, **23,** 313
9 Pèpe, G., Reboul, J.P., Cristau, B. and Oddon, Y. *Eur. J. Med. Chem. Ther.-Chim. Ther.* 1986, **21,** 339
10 Pèpe, G., Reboul, J.P. and Oddon, Y. *Eur. J. Med. Chem. Ther.-Chim. Ther.* 1989, in press
11 Paulus, E.F. *Acta Cryst.* 1978, **B19,** 1942
12 Colleagues interested in installing MolPot on their own computers should request further information from the author