

## Topological Properties of the Molecular Electrostatic Potential as a Tool for Prediction of Biological Activity

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**Abstract.** The paper is an attempt to reveal a relation between the structure and biological activity. Topological properties of molecular electrostatic potentials were investigated. These properties are represented by tree graphs. Based on known experimental data concerning biological activity of a series of various compounds, a relation between the biological activity and the characteristics of the tree graph was searched for. Such a relation might be used to predict biological activity of compounds other than investigated. Characteristic graphs are presented enabling prediction of activity of compounds.

**Key words:** Molecular electrostatic potential — Structure-activity relationship

### Introduction

Molecular electrostatic potential (MEP) of distribution of electronic and nuclear charges calculated on different levels of approximation (Scrocco and Tomasi 1973) has widely been used in recent years as a chemical reactivity index to study interactions between molecules and ions or solvents and biological properties of molecules. The work of Peinel and coworkers (1980) can be mentioned as an example of application of MEP to the prediction of molecular electrostatic interaction properties. A survey of MEP applications (including a study of biological activity) is presented in the paper by Petrongollo (1978).

Prior to considering topological properties of MEP, the difference between “chemical” and “biological” activity of a particular molecule should be explained. In studying chemical activity (reactivity), interactions between a given and other molecules are investigated, while in studying biological activity, the interaction of a series of molecules with the same environment (i.e., a biological receptor) is investigated. It is obvious that the ability of a molecule to reach a biological receptor in a juxtaposition, is determined by long-range forces, i.e. electrostatic forces. This is a precondition for any biological activity. The biological effectivity is

then determined by both the quality and intensity of interaction between the biologically active molecule and the receptor to some extent in analogy to chemical reactivity. It is obvious that if this condition is not met no biological activity can occur. Thus for characterisation of chemical reactivity the local properties of MEP (reactivity indices) are important while global properties of MEP are important to characterise biological activity.

MEP is a function of three independent variables; it can be interpreted as a hypersurface in a four-dimensional space with three cartesian coordinates, and the value of MEP itself as the fourth dimension. Global properties (shape) of an arbitrary function of  $n$  independent variables can be characterised by relations between its "characteristic" points (extrema, saddle points), i.e. by a topology of particular  $n + 1$  dimensional hypersurface. Accordingly, a hypothesis may be formulated: it can be expected that for all biologically active molecules which act on the same receptor by the same mechanism, some common feature in the topology of their MEPs should exist.

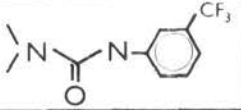
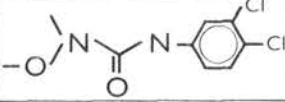
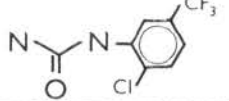
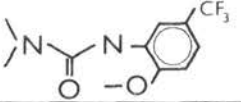
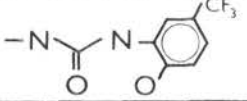
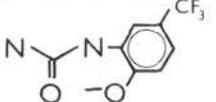
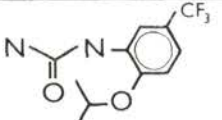
## Methods

There are several different possibilities how to express the shape of MEP in a three-dimensional space. A series of two-dimensional cuts has been the most frequently method used. This method is convenient when MEP is used as reactivity index, or to predict possible interactive regions of a molecule during interactions with ions or dipoles. However, the topological properties of the MEP four-dimensional hypersurface are difficult to extract from such a two-dimensional cut.

Another way of drawing the shape of MEP is a stereoprojection of isopotential surfaces. By this technique the MEP shape can be described by a series of drawings for different MEP values. This method, however, puts high demands on computer graphics and interpolation procedure. Perspective views on isopotential shells are more instructive than maps of two-dimensional cuts and, moreover the topological information is easier to obtain from a series of these pictures than from the maps of two-dimensional cuts. Both methods of MEP visualisation mentioned above include information concerning local properties of MEP hypersurface in addition to the topological information.

A method of visualisation of pure topological properties of an arbitrary  $n$ -dimensional hypersurface was suggested by Zhuravlev and Krivoshey (Zhuravlev et al. 1975; Krivoshey and Sleta 1974). According to this method, each MEP can be represented by a tree graph with labeled vertexes, being topologically equivalent to MEP hypersurface. In this form, the MEP topological properties are highly instructive and differential properties are entirely neglected. The vertexes of the tree correspond to important points of MEP hypersurface and they are labeled by MEP values at these points.

All the hitherto published papers have investigated the relation between biological activity of a particular molecule and its MEP, using methods of MEP visualisation which provide mixed information on both global and local properties. The weight attributed to the importance of local or global properties of MEP has not been specified and it has depended on individual, and mostly intuitive, views of the problem studied. Visualization of topological properties of MEP hypersurface replaces the intuitive procedure by a two-step technique. In the first step, global properties of MEP hypersurface are established and conditions for biological activity are derived. These conditions are determined on the basis of known experimental data on biological activity of molecules of the series investigated as characteristics of MEP graph which are common for active compounds and which does not occur in

I		+
II		+
III		+
IV		-
V		-
VI		-
VII		-

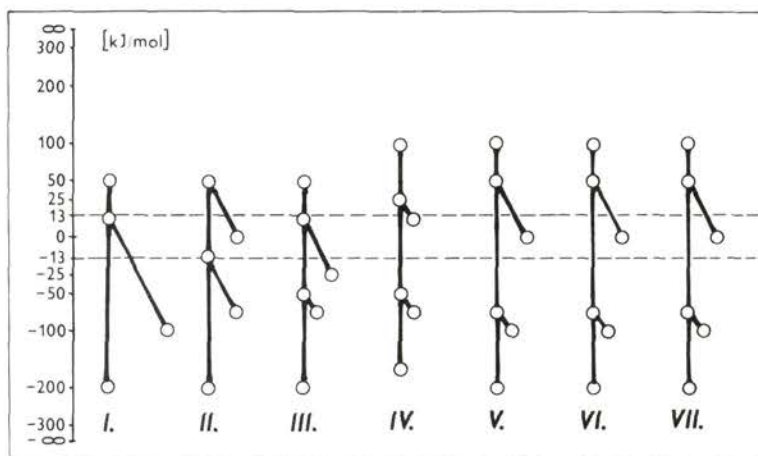
**Table 1.** Inhibitors of Hill's reaction studied. Active (+) and inactive (-) compounds.

inactive compounds. In the second step, which takes into account MEP local properties and other parameters commonly used in structure-activity analysis, quantitative relations between the biological activity and the molecular structure are studied in a subgroup of molecules which meet the requirements derived from topological investigation of MEP in the first step.

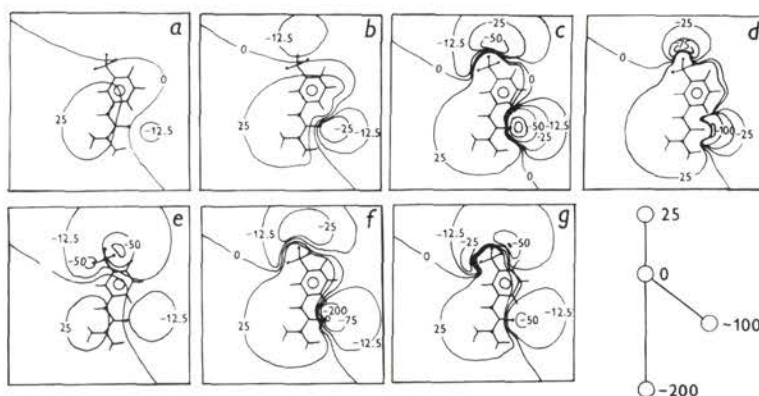
### Application

Let us present applications on a group of active molecules of pesticides and on another of local anaesthetics of the first step of the procedure suggested above. Table 1 shows a list of herbicides active as inhibitors of Hill's reaction giving their biological activities. The most stable conformations of the molecules studied were calculated by the PCILO method (Diner et al. 1969a, b; Jordan et al. 1969; Malrieu et al. 1969) and using CNDO/2 (Pople and Beveridge 1970) wavefunctions of the most stable conformers the particular MEPs were calculated (Mocko et al. 1984). The tree graphs which are topologically equivalent to the particular MEP



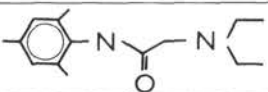
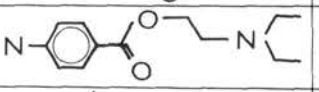
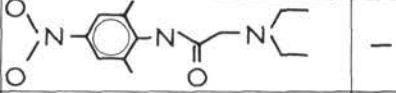
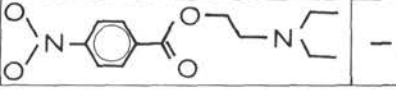


**Fig. 1.** Graphs of MEP-hypersurface of the studied inhibitors of Hill's reaction. Denotation corresponds to that in Table 1.



**Fig. 2.** Maps of molecular electrostatic potential of the fluometuron molecule (molecule I, Table 1). The benzene ring is sited in the xy-plane, the z-coordinates of the cut a, b, c, d, e, f, is  $-.3; -.2; -.1; 0; .1; .2; .3$  nm, respectively. Energy is expressed in kJ/mol.

hypersurfaces are shown in Fig. 1. The vertices were labeled according to their position on the energy axis. Since MEP values may range from  $-\infty$  to  $+\infty$ , the energy axis was calibrated using the relation  $A \cdot \tanh(kE)$ , where  $A$  is 50% of the energy axis length on the graph, and  $k$  is a constant selected so as to get the energy scale approximately linear in the region which seems to be interesting for the series of molecules studied.  $E$  is a particular value of MEP. The sections of the graph which correspond to Coulombic repulsion in the nuclear vicinity have not been

I		+
II		+
III		-
IV		-

**Table 2.** Local anaesthetics and their inactive analogues studied. Active (+) and inactive (-) compounds.

shown as the calculation of MEP values at distances shorter than van der Waals radius seems to be superfluous for on a shorter distance interacting systems cannot approach each other. Figure 2 shows 7 cuts of electrostatic potential of fluometuron. The individual graphs on Fig. 1 cover the same amount of topological information as do the series of MEP cuts presented in Fig. 2. It is obvious that Fig. 2 contains a mixed information on both local and global properties of MEP hypersurface; however, a separation is rather difficult. From the graph for the fluometuron molecule it is obvious that there exist two regions of proton attraction separated by an energy barrier. The graph provides information necessary for topological evaluation of MEP in a much more condensed form. Comparing graphs for active and inactive derivatives (Fig. 1) it can be seen that the existence of a saddle point on MEP hypersurface with an energy ranging from  $-13$  to  $+13$  kJ/mole is a common feature for active derivatives.

Table 2 contains a list of highly efficient local anaesthetics and their inefficient nitroanalogs (Galinsky et al. 1963). The energetically optimal conformations were determined by the PCILO method and the particular MEPs were calculated using CNDO/2 wavefunctions. Fig. 3 shows graphs topologically equivalent to the MEP hypersurfaces. Both, the energetic scale and the calibration function are the same as in Fig. 1. The apparent differences in branch formation in active and inactive derivatives are clearly seen in Fig. 3.

## Conclusions

Great differences found in the graphs of MEP hypersurfaces between active and inactive derivatives for two groups of compounds with entirely different biological activity shows that hypersurface topological properties of MEP can be a reliable

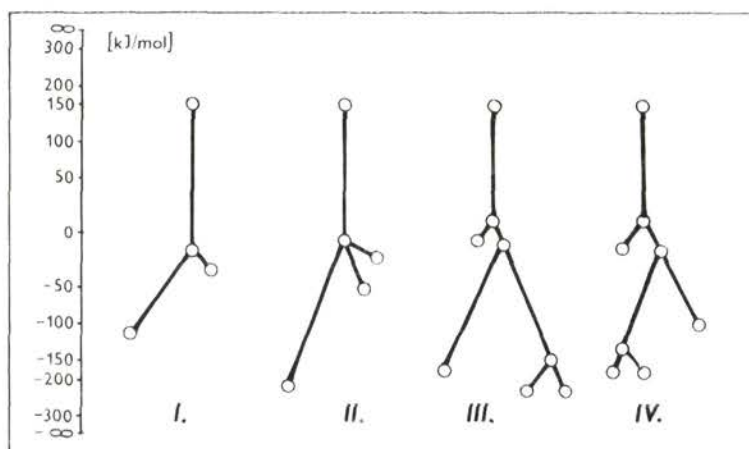


Fig. 3. Graphs of MEP-hypersurface of local anaesthetics and their inactive analogues studied. Denotation corresponds to that in Table 2.

tool for the study of biological activity of molecules. With respect to the small number of molecules in the series studied, the aim of the presented paper was not to define exact criteria for the biological activity of investigated molecules. Rather we should turn attention to the importance of global properties of MEP in the interaction of a molecule with the biological environment (receptor). The method presented in this work seems to be a reliable procedure for evaluation global properties of MEP hypersurface which play a key role in initial steps of the interaction of a molecule with the biological receptor.

**Acknowledgement.** The helpful discussion and comments of Dr. P. Baňacký on the paper is acknowledged.

## References

- Diner S., Malrieu J. P., Claverie P. (1969a): Localized bond orbitals and the correlation problem. I. The perturbation calculation of the ground state energy. *Theoret. Chim. Acta* **13**, 1—17
- Diner S., Malrieu J. P., Jordan F., Gilbert M. (1969b): Localized bond orbitals and the correlation problem. III. Energy up to third order in the zero-differential overlap approximation. Application to  $\pi$ -electron systems. *Theoret. Chim. Acta* **15**, 100—110
- Galinsky A. M., Gearien J. E., Perkins J., Susina S. V. (1963): Electronic effects of para-suituents on the local anaesthetic activity of 2-diethylamino benzoate and related compounds. *J. Med. Chem.* **6**, 320—322
- Jordan F., Gilbert M., Malrieu J. P., Pincelli U. (1969): Localized bond orbitals and the correlation problem. IV. Stability of the perturbation energies with respect to bond hybridization and polarity. *Theoret. Chim. Acta* **15**, 221—224
- Krivoshay I. V., Sleta L. A. (1974): A topological stochastic approach to the study of multidimensional potential energy surfaces of chemical reaction. *Theoret. Chim. Acta* **43**, 165—174

- Mairieu J. P., Claverie P., Diner S. (1969): Localized bond orbitals and the correlation problem. II. Application to  $\sigma$ -electron systems. *Theoret. Chim. Acta* **13**, 18—45
- Mocko V., Fiedler K., Leška J. (1984): Quantum chemical study of pesticide active derivatives of phenylurea I. Equilibrium geometries. *Coll. Czech. Chem. Commun.* **49**, 190—196
- Peinel G., Frischleder H., Birnstock F. (1980): The electrostatical molecular potential—a tool for the prediction of electrostatic molecular interaction properties. *Theoret. Chim. Acta* **57**, 245—253
- Petrongollo C. (1978): Quantum chemical study of isolated and interacting molecules with biological activity. *Gaz. Chim. Ital.* **108**, 445—478
- Pople J. A., Beveridge D. L. (1970): *Approximate Molecular Orbital Theory*. Mc Graw-Hill, New York
- Scrocco E., Tomasi J. (1973): The electrostatic molecular potential as a tool for the interpretation of molecular properties. *Top. Curr. Chem.* **42**, 95—170
- Zhuravlev V. I., Krivoshey I. V., Sleta L. A. (1975): General properties of multidimensional surfaces of the potential energy of chemical reaction. *Zh. Struct. Khim.* **16**, 951—955 (in Russian)

Received March 22, 1983/Accepted January 10, 1984