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APPROXIMATE MOLECULAR ELECTROSTATIC POTENTIALS OF PROTONATED MESCALINE ANALOGUES

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ABSTRACT. The molecular electrostatic potential maps of five protonated phenylethylamines have been calculated and compared with that of protonated serotonin. Protonation leads to a very similar potential area around the amine chain in all the molecules suggesting that this region may serve for the orientation and / or the interaction with the serotonergic receptor. It was not possible to obtain a qualitative relation between hallucinogenic potency and electrostatic potential values.

INTRODUCTION

In a recent paper (1), Kier et al. presented a study of the molecular electrostatic potential maps of five substituted phenylethylamines. They found a correlation between the hallucinogenic potency of four phenylethylamines and the decline of the electrostatic potential value which is located in the region between the 3 and 4 phenyl positions.

At physiological pH, 95% of adrenaline, noradrenaline and dopamine exist as cations and the protonation of the nitrogen atom is essential for efficiency (2). As the phenylethylamines analyzed by Kier et al. (1) in their basic form are similar to the above ones and also are highly ionized at physiological pH (3), in the present work the molecular electrostatic potentials (MEP) of these protonated forms have been examined.

Considering that the MEP map generated around the pharmacophorically significant parts of the phenylethylamines must resemble in shape to the potential generated around the neurotransmitter itself (serotonin in this case), the analogies and

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differences observed should contribute to a better understanding of the interaction with the receptor.

Furthermore, a correlation factibility between *in vivo* (hallucinogenic) activity and potential value is examined.

METHODS

The MEP at point **r**, V(**r**), is defined by (in a.u., Ref. (4)):

$$V(\mathbf{r}) = \sum_a Z_a(\mathbf{r}-\mathbf{R}_a)^{-1} - \sum_r \sum_s P_{rs} \langle X_r(\mathbf{r}_1) | (\mathbf{r}-\mathbf{r}_1)^{-1} | X_s(\mathbf{r}_1) \rangle \qquad / 1 /$$

where P_{rs} is an element of the population matrix, Z_a is the core charge of atom a and X refers to atomic orbitals. The molecular electrostatic potential represents, in a first order approach, the interaction energy of the molecule with an unitary positive charge located at **r**.

It is possible to obtain a point-charge representation of the MEP , employing the following expression:

$$V(\mathbf{r}) = \sum_t Q_t \, |\mathbf{R}_t - \mathbf{r}|^{-1} \qquad / 2 /$$

where Q_t is the net charge of atom t and $|\mathbf{R}_t - \mathbf{r}|$ is the distance between atom t and point **r**. Oie et al. (5) have employed equation /2/ to study the MEP of large molecules (i.e. ethyl chlorophyllide a, of about 80 atoms, including Mg, N and O). They compared the results with the ones obtained employing equation /1/ within an *ab initio* calculation (5). It was found that, inside the van der Waals sphere, the results obtained with equation /2/ do not have physical meaning. Beyond the van der Waals radius, they found that the MEP maps are qualitatively well described by equation /2/ (see also Refs. (6) and (7)).

The calculation of the net charges was carried out in the framework of the molecular orbital theory at the CNDO/2 level, with the program CNINDO (QCPE 141). We employed bond distances and bond angles from Niemeyer's work (8). For the sake of comparison, we have placed the amine side chain and the phenyl ring substituents in the same position as in Kier's work (see Ref.(8) for a résumé of conformational studies on these kind of molecules). The resulting CNDO/2 wave functions were subjected to an inverse Löwdin transformation to yield deorthogonalized wave functions (9). Later, a Mulliken population analysis (10) was performed and the resulting net charges were employed in equation /2/ to compute the MEP in the plane of the phenyl ring.

RESULTS AND DISCUSSION

Figures 1 to 5 show the potential maps of the phenylethylamines studied. Figure 6 displays the MEP of protonated serotonin. The units employed are Kcal/mol.

From an inspection of these figures it can be observed that the protonation changes strongly the form of the potential field respect to the basic form (Ref. (1)). Furthermore, in all the maps it is possible to distinguish three very different field regions (see the figures):

1. First: a kind of positive potential *hat* surrounding the amine chain and part of the benzene ring.
2. Second: an intermediate region, comprising the C-2 and C-6 atoms (see Fig. 1).
3. Third: a region which includes the C-3, C-4 and C-5 atoms.

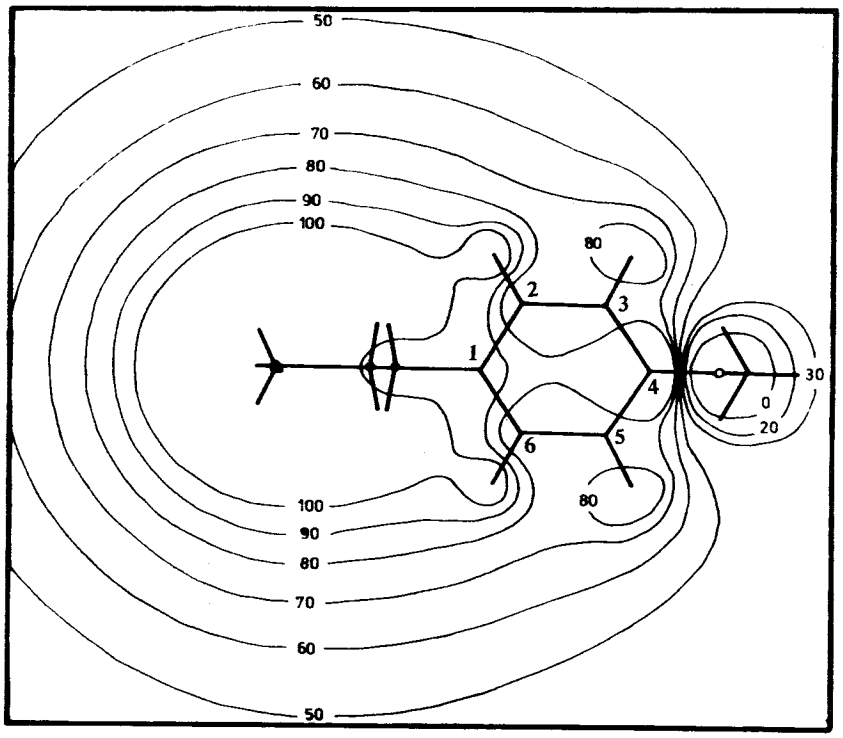

Figure 1
MEP map of the protonated p-methoxyphenylethylamine in the aromatic molecular plane.

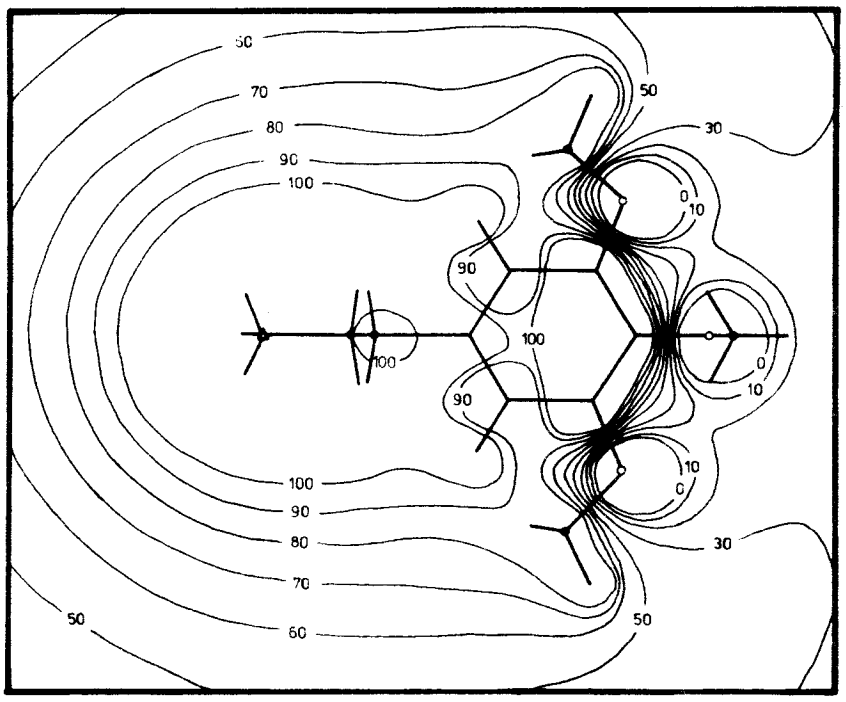

Figure 2
MEP map of the protonated 3,4,5-trimethoxyphenylethylamine (mescaline) in the aromatic molecular plane.

In all the figures can be easily appreciated that the first region of the phenylethylamines is very similar. This feature strongly suggest that this region may serve for the recognition of the drug by the receptor at a distance greater than that at which conformational and electronic perturbation ensue (11)

In the second region, one interesting fact emerges: in the 2,5-dimethoxy-4-methylphenylethylamine, the most active of the molecules studied (Figure 5), the potential field is almost the same as that in serotonin (Figure 6). Remembering that these molecules act as competitive antagonists, this similarity in the MEP maps may explain the high potency of this molecule (see Ref. (1) for values).

The third region is the only one where the protonation has not produced a similar field structure in all the molecules. Its shape depends on the position and nature of the substituents. These three region have been found in 34 phenylethylamines, phenylisopropylamines and tryptamines analyzed (results for tryptamines see Ref.(12) and for phenylalkylamines see Ref.(13)).

From receptor theory we know that a high degree of complementary between the drug and the receptor is required. This high degree of specificity permits the

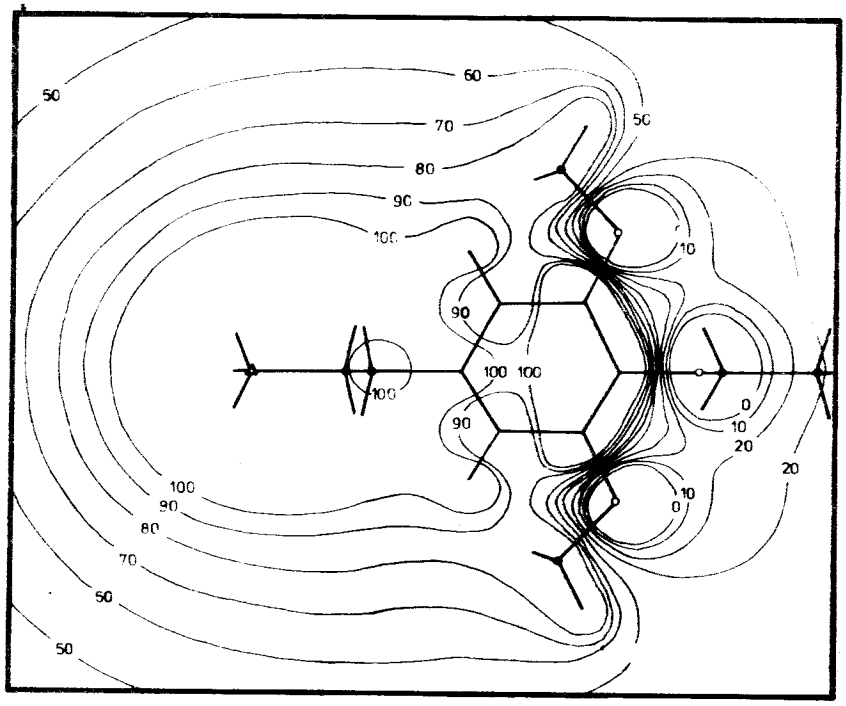

Figure 3
MEP map of the protonated 3,5-dimethoxy-4-ethoxyphenylethylamine in the aromatic molecular plane.

drug to approach the receptor after the recognition, and to form the drug-receptor complex through van der Waals forces, hydrogen bonding, charge transfer, etc. (14).

As the principal differences in the MEP of the drugs analyzed appear in the last two regions, we suggest that they are probably connected with the strengh of the drug-receptor interaction, regulating the activity of these molecules.

Our next step was to try to obtain a relation between hallucinogenic potency and field values in some points, as in Kier's work. We selected points located near the points proposed by Kier et al. (1) (but beyond the van der Waals sphere), and points close to the para substituents. Our analysis showed that it is not possible to find out a simple relation between hallucinogenic potency and field values. The two main reasons of this failure are:

1. The hallucinogenic potency is an *in vivo* measure, including factors like absorption, transport, metabolism, excretion, etc. These factors determine the relation between the dose of the drug and its concentration in the biophase, and they are not equal in all the molecules. Considering that the magnitude of the effect produced

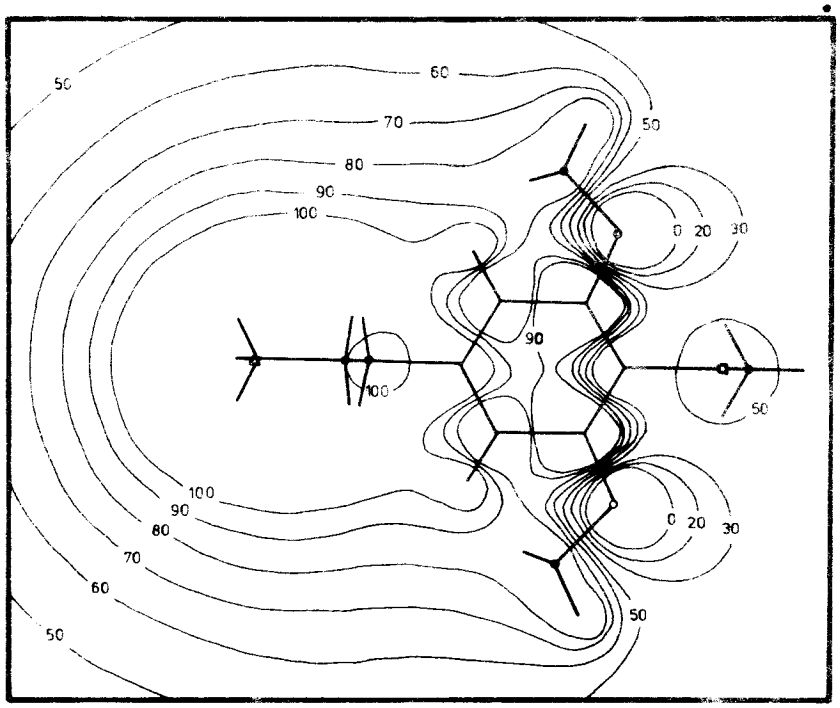

Figure 4
MEP map of the protonated 3,5-dimethoxy-4-methylphenylethylamine in the aromatic molecular plane.

by a drug depends on the concentration of drug-occupied receptors and that the pattern of the electrostatic potential map can only be studied as a template for the matching interactions with the receptor, it seems to us that relations between *in vivo* activity and electrostatic potential features are devoid of physical meaning.

2. Accepting the hypothesis of a *cationic head-anionic center interaction* as in Kier et al.'s work (1), it is clear from our study that the main purpose should be the orientation of the molecules at long distances. By following, the neutralization of the cationic head will be achieved progresively and at short distance. Thus at this level, all the rest of the molecule will be in interaction and the structure of the potential around the molecule can become very different from that of the protonated and basic forms.

Kier et al. (1) worked with molecules in their basic form which exists in a very small quantity in the biophase (3). The reasons for his choice seem to be based on the assumption that the cationic head of these molecules is directly invol-

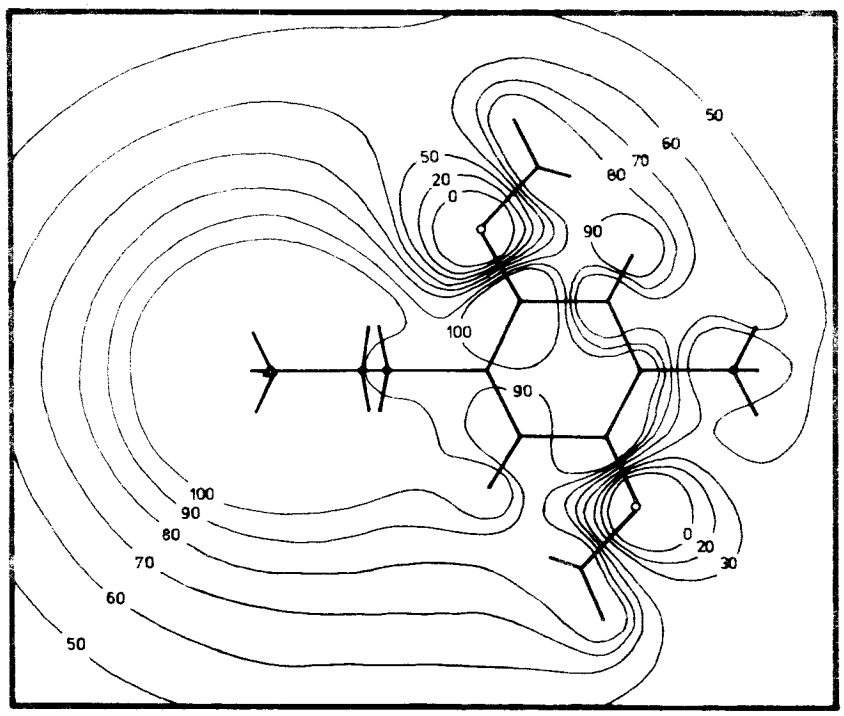

Figure 5
MEP map of the protonated 2,5-dimethoxy-4-methylphenylethylamine in the aromatic molecular plane.

ved in an interaction with an anionic site of the receptor. Weinstein at al. (15) showed that *such kind of interaction confers on the electronic structures of the molecules all the major characteristics of the neutral species* (taken from Ref. (15). See this reference and bibliography therein for a resumé). These arguments do not seem to us a sufficient reason to carry out the study on the basic form (see point 2). On the other hand, their correlation was obtained on the basis of electrostatic potential values for points located inside the van der Waals' sphere, however calculations with equation /2/ have not physical meaning for points inside the sphere (5), therefore it seems rather surprising that a correlation appears.

In conclusion, the results of this work allow us to suggest that the main effect of the protonation in this kind of molecule is probably to produce an uniform electrostatic potential around it, permitting its recognition by the receptor through long-range forces. Also, we must add that in the phenylethylamines and phenylisopropylamines, the meta substituents adopt a conformation imitating the five-membered ring of serotonin (16).

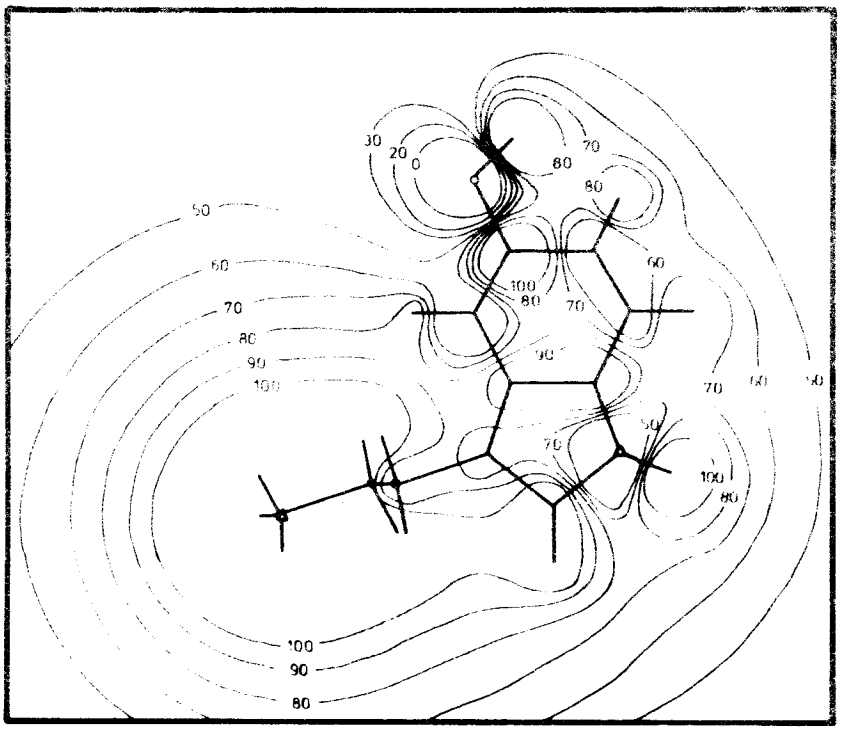

Figure 6
MEP map of the protonated 5-hydroxytryptamine (serotonin) in the aromatic molecular plane.

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