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Approximate Molecular Potentials of Mescaline Analogues in a Study of Similarities to 5-Hydroxytryptamine

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SUMMARY

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The electrostatic potentials of five substituted phenethylamines have been calculated and compared with that of 5-hydroxytryptamine (5-HT). A common pattern of potentials was found in four of the five phenethylamines and 5-hydroxytryptamine which is associated with a previously postulated 5-HT pharmacophore. These four analogues are qualitatively reported as being hallucinogenic; the fifth analogue is not. A quantitative relationship was found between the hallucinogenic potency in the four phenethylamines and the decline of a negative electrostatic potential in the region between the 3 and 4 phenyl positions, reinforcing previous reports on the quantitative importance of this part of the molecule.

INTRODUCTION

Ring-substituted phenethylamines such as mescaline and others have a low to modest degree of potency as human hallucinogenic agents (1) (Table 1). The mechanism by which these and other amines such as amphetamines and tryptamines exert their CNS effect is not yet known, though there is evidence which implicates 5-hydroxytryptamine (serotonin) receptors in this phenomenon (2, 3). Both mescaline and DOM were found to share the inhibitory effect of LSD on the rate of firing of neurons in the dorsal and median raphe nuclei in rats by Foote *et al.* (4). Wallach *et al.* (5) also suggested that DOM appears to act on the LSD receptor. Dyer (6) and Barfknecht *et al.* (7) have suggested that psychotomimetic activity of phenalkylamines may be related to stimulation of serotonin receptors. Recently Glennon *et al.* (8) have found that the potency of several methoxylated phenethylamines paralleled their binding affinities to rat stomach fundus, rich in 5-HT receptors. From molecular orbital conformational predictions, Kang *et al.* (9) found that a spatial congruence between mescaline and 5-hydroxytryptamine was possible from energy considerations.

If these molecules produce their hallucinogenic effect at a central 5-HT receptor, then we might anticipate structural similarities between the potent phenethylamines and 5-HT. Further, if the response of these molecules is related to the strength of interaction with the receptor, by virtue of a stereochemical and/or electronic congruence, as indicated by the work of Glennon *et al.* (8), then a relationship between potency and the electrostatic fields might be discernable. To shed further light on the structure–activity relationships of the mescaline analogues and to further test the hypothesis of 5-HT receptor involvement, we have selected several mescaline analogues (Table 1) for study of their electrostatic potential fields, in comparison with the field for 5-hydroxytryptamine.

APPROXIMATE MOLECULAR POTENTIALS

In the past several years a number of studies have appeared in which the electrostatic potential surrounding a molecule has been used to predict active sites for protonation and even alkylation. The early work by Bonaccorsi *et al.* (10) has been followed by contributions from Weinstein, and co-workers (11, 12) and applications by Rein *et al.* (13), Kier and Aldrich (14), Bonaccorsi *et al.* (15), and Poltizer and Daiker (16). Related electron density studies by Breon *et al.* (17) were also accompanied by approximately potential plots for several large narcotic compounds including morphine. These studies indicate a rapid growth in the use of molecular potential maps to assess structure activity relationships.

The electrostatic potential at any particular point in space around a molecule is defined rigorously in atomic units by $V(r)$ in Eq. [1], where Z_a and R_a refer to specific atomic nuclei and $\rho(r)$ is the electronic density.

$$V(r) = \sum_a \frac{Z_a}{|R_a - r|} - \int \frac{\rho(r')dr'}{|r - r'|}. \qquad [1]$$

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TABLE 1

Phenethylamines considered in study

Figure	Position/substituent	Potency	Electrostatic potential at point D in Figs. 1–5
		mescaline units	*kcal/mol*
1	4-Methoxy	<1	
2	3,4,5-Trimethoxy (mescaline)	1	−40
3	3,5-Dimethoxy-4-ethoxy	7	−32
4	3,5-Dimethoxy-4-methylthio	12	−23
5	2,5-Dimethoxy-4-methyl	20	−3

As Kaufman and Koski (18) have pointed out in a recent review, several levels of approximation are available for $V(r)$. Several comparisons have been made between rigorous potentials at near-Hartree–Fock levels and less rigorous but more easily computed approximate maps by Scrocco and Tomasi (19) and Giessner-Prettre and Pullman (20). For very large molecules, the general integral of the second term of Eq. [1] requires enormous amounts of computer time due to the large number of three center nuclear attraction integrals which occur at each grid point. The classical or coulombic potential at each point is rapidly computed employing Eq. [2] even for very large molecular systems where Q_a is the net atomic charge at each atomic site. As noted by other workers (19, 21), a point charge model,

$$V(r) = \sum_a \frac{Q_a}{|R_a - r|}, \qquad [2]$$

tends to be too extreme right at the atomic sites, an effect which is easily suppressed, but beyond the chemically significant van der Waal's radius, the simple map is qualitatively correct. While σ and π charges are collapsed into a single point charge here, potentials computed in an aromatic plane conveniently measure a *net* attraction or repulsion of a proton by that atom site. Approximate potential regions are generally less diffuse than those derived directly from the wave function, and minima tend to be too shallow, as well as too isotropic close to atoms. Thus, while some directional character is lost by using point charges, the relative magnitudes of potential minima are well defined so that cation and protonation sites may be predicted. In general, the model remains useful when searching for similar features in large molecules, particularly if used in conjunction with structural information and biological data for interactions of 10 to 100 kcal. Most important, we have an easy way to compare the "potential chemistry" of the outer surface of a molecule, both the electrostatic potential and the potential capability of various sites for chemical interaction.

METHODS

Calculations on all compounds were performed using program CNINDO (QCPE 141), enlarged to treat 100 valence shell orbitals. The resulting CNDO/2 wave functions were then subjected to an inverse Löwdin transformation (22) to yield the deorthogonalized wave functions (23). A Mulliken charge analysis was then performed (24). The resulting atomic charges were then used in Eq. [2] to compute the classical electrostatic potential for each molecule. Potential values were printed initially in place on a line printer map as integer values (14) so field-overflow asterisks conveniently suppressed high values very near atomic sites.

Potential maps for 5-HT and a series of phenethylamines (mescaline analogues) were computed using Eq.

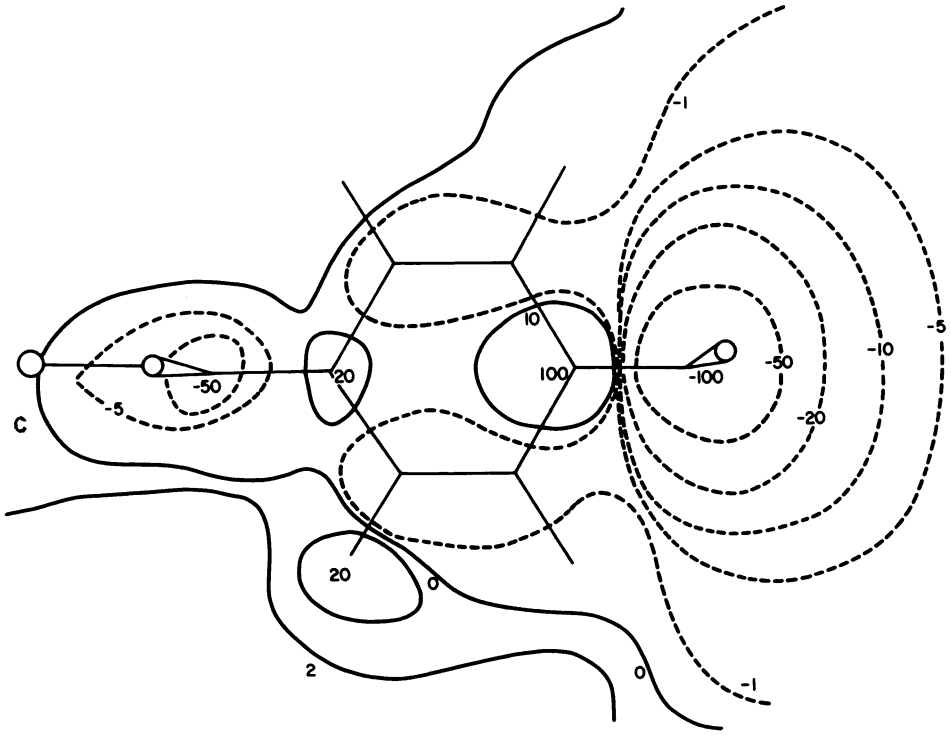

FIG. 1. I. *Approximate electrostatic potential for p-methoxyphenethylamine in kcal/mol*

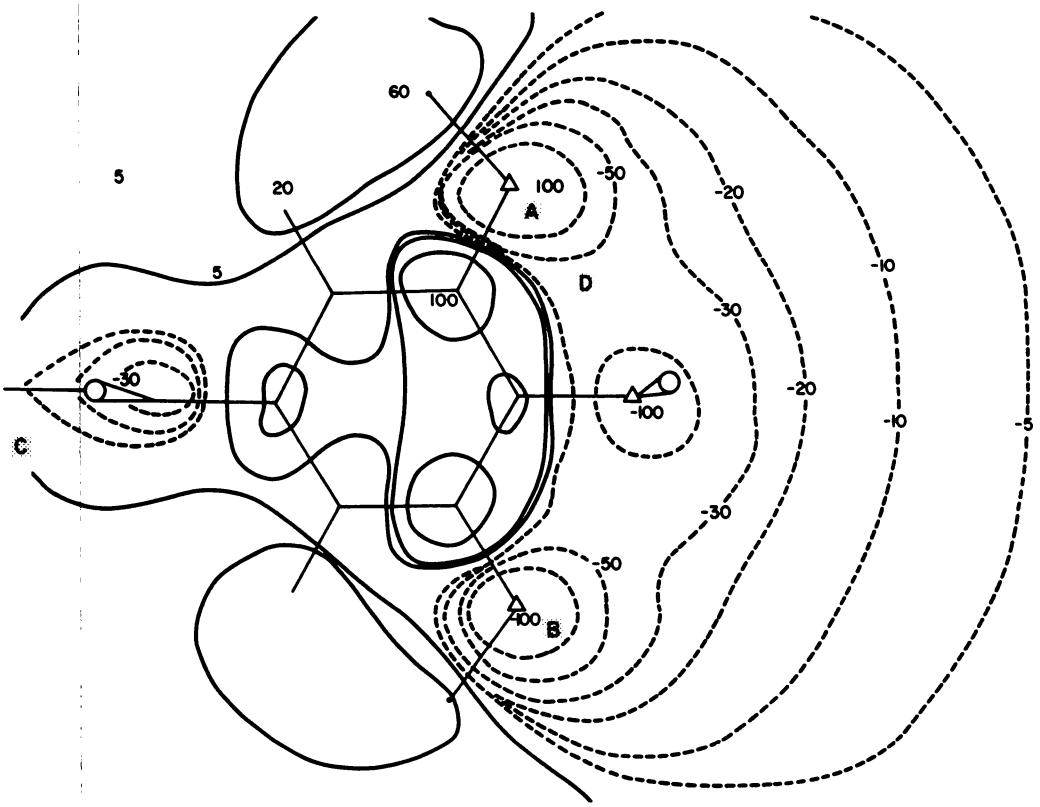

FIG. 2. II. *Approximate electrostatic potential for mescaline in kcal/mol*

[2] as described above, and redrawn by interpolation between equipotential points. Coordinates for the phenethylamines were obtained using crystallographic data of Bergen (25). The fully extended ethylamine side chain was used for all compounds in agreement with *ab initio* calculations by Martin *et al.* C–S bond lengths for sulfur were experimental values taken from Abrahams (27). Methoxy groups in mescaline were taken to have the two meta groups lying in the aromatic plane, with their mutual ortho group at right angles to the plane as indicated by crystallographic data (25). The substituent group in the other phenethylamines was taken to be at right angles to the aromatic ring (except for compound V which is methyl substituted), with the other methoxy groups lying in the plane of the aromatic ring. These conformations are in agreement with PCILO conformational studies and photoelectron spectral data for methoxylated benzenes (28).

Potential maps shown here were computed in the plane of the aromatic ring for 5-HT and for five different substituted phenethylamines of known hallucinogenic activity. A total of 13 maps per molecule was computed from 3 Å below the plane of the aromatic ring to 3 Å above. From 2.0 Å above (toward the amine side chain) to 2.0 Å below, the prominent potential patterns showing minima 5–6 Å apart (A, B) were found in 5-HT and the phenethylamines II–V. To minimize the number of maps presented and to best illustrate the electrostatic similarities as well as the 4-substituent effects, only the maps computed in the plane of the aromatic ring are presented here. The compounds studied were *p*-methoxyphenethylamine (I), mescaline (II), 3,5-dimethoxy-4-ethoxyphenethylamine (III), 3,5-dimethoxy-4-methylthiophenethylamine (IV), and 2,5-dimethoxy-4-methylphenethylamine (V), in order of increasing activity. Activity data were from human subjects and are expressed as mescaline units as defined by Shulgin and co-workers (1, 29). A mescaline unit is defined as the ratio of the dosage (mg) of mescaline (350 mg) required to produce a hallucinogenic response to the dosage (mg) of the compound in question required to elicit the same response.

Studies were undertaken in two areas. First, we wished to determine whether or not the hallucinogenic phenethylamines showed any similarity to 5-HT (serotonin) in their electrostatic potential fields. Such a similarity may indicate a possible receptor equivalence, although one could not preclude other possible receptors. Electrostatic similarities would simply suggest the possibility of receptor equivalence and would support the suggestions of other workers (2–8) as to this likelihood.

The second part of the study was a search for a relationship between changes in a part of the electrostatic field within the series of molecules and the potency.

The potentials for neutral amines were computed following Weinstein and Osman (12) and Martin *et al.* (26). This model portrays the cationic head of the amines anchored at one part of the receptor site, with the molecule taking on the electronic features of the neutral amine. Subsequent orientation and activity at the receptor should then be the same as those of the neutral species.

RESULTS AND DISCUSSION

In order to compare the phenethylamines with 5-HT,

certain criteria must be established in terms of the electrostatic potentials of the molecules studied. Figure 6 reveals the electrostatic potential map for 5-HT calculated as described in a previous section. Three prominant regions can be identified, which correspond to the pharmacophore proposed earlier by Kier (30) and by Kelley and Adamson (31). These include the region of the 5-hydroxyl group, labeled A; the region of the indole nitrogen, labeled B; and the region of the amino nitrogen, labeled C. The first two regions defined here by the −50 kcal contour in 5-HT are strongly negative, while the third region is associated with the amine group.

If these regions comprise the essential features of the molecule, by definition the pharmacophore, then complimentary features might be postulated on the receptor, capable of efficacious interaction to produce a response. It follows that an agonist molecule, a molecule acting efficaciously at the same receptor, should have a comparable pattern of electrostatic potentials. It should be stated that the possession of a comparable pharmacophore is hypothesized to be a necessary but not a sufficient requirement for 5-HT-like potency.

For the phenethylamines to possess 5-HT potency, then, a comparable pattern of potentials should be found. Figures 1–5 show the computed potentials for five phenethylamines ranging widely in potency. Molecular potentials in Fig. 2–5 reveal a trio of regions and charges comparable to those exhibited by 5-HT in Fig. 6. The qualitative activity of these four analogues is the same, that is, all four are rated to be hallucinogenic agents. In contrast, the potential map of the 4-methoxy analogue shown in Fig. 1 reveals an absence of regions comparable to A and B in 5-HT. The hallucinogenic activity and 5-HT receptor affinity of this molecule is low.

The comparisons suggest that the presence of these three regions in the electrostatic potential maps, comparable to 5-HT, may be associated with hallucinogenic activity and that the activity may be occurring at a receptor responsive to 5-HT. The quantitative differences in potency for analogues II–V must now be accounted for within the structural descriptions provided by these electrostatic potentials. Inspection reveals that the region between substituents on the 2 and 4 positions varies through the series in Figs. 2–5. To confirm this, a point common to all four molecules was located 1.2 Å perpendicular to the midpoint of the 3–4 ring bond and in the plane of the ring, labeled D. The electrostatic potential at this point was calculated to become less negative through the series of molecules in Figs. 2 through 5.

A decrease in the magnitude of the field between positions 3 and 4 parallels an increase in hallucinogenic activity. These findings are in agreement with those of DiPaolo *et al.* (32), who found that the presence of negatively charged substituents in the 3,4 positions correlated with a decrease in activity within a large group of hallucinogenic phenylisopropyl amines. Our findings are also compatible with the findings of Glennon *et al.* (8) and Nichols *et al.* (33) about the influence of the 4-position substituent. This substituent has been suggested as influencing a favorable hydrophobic interaction at the receptor, the corollary being inferred that a polar moiety at 3 or 4 would adversely influence the receptor binding at this region. An alternative possibility may be that the

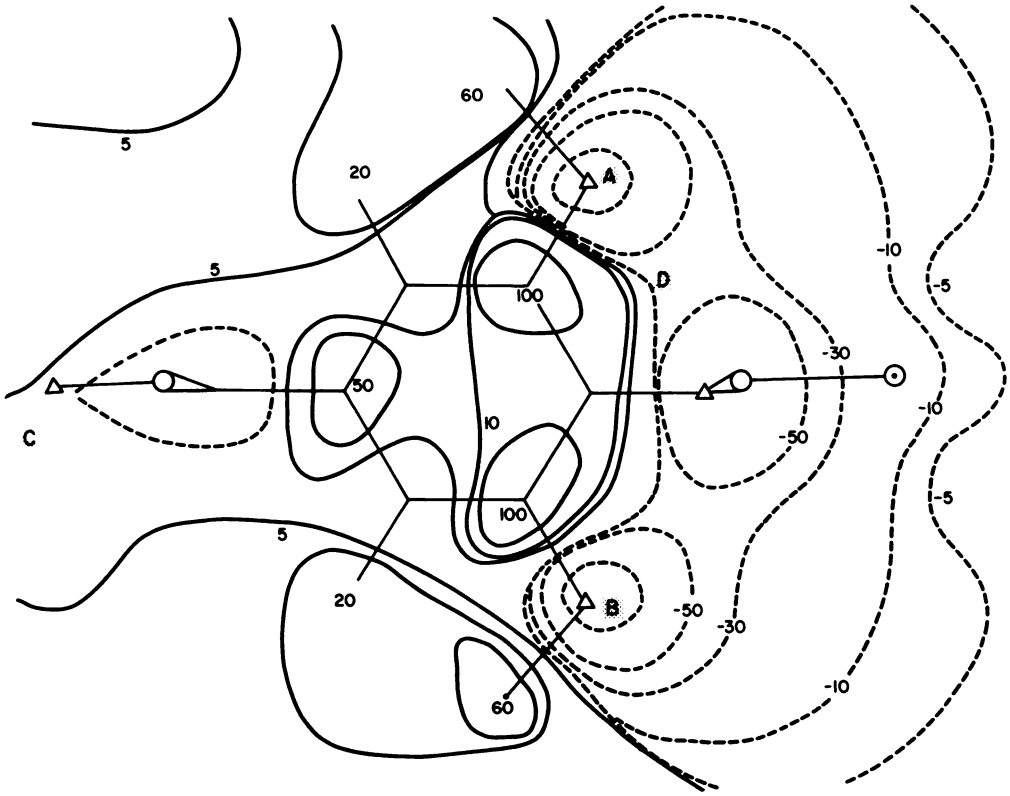

FIG. 3. III. *Approximate electrostatic potential for 3,5-dimethoxy-4-ethoxyphenethylamine in kcal/mol*

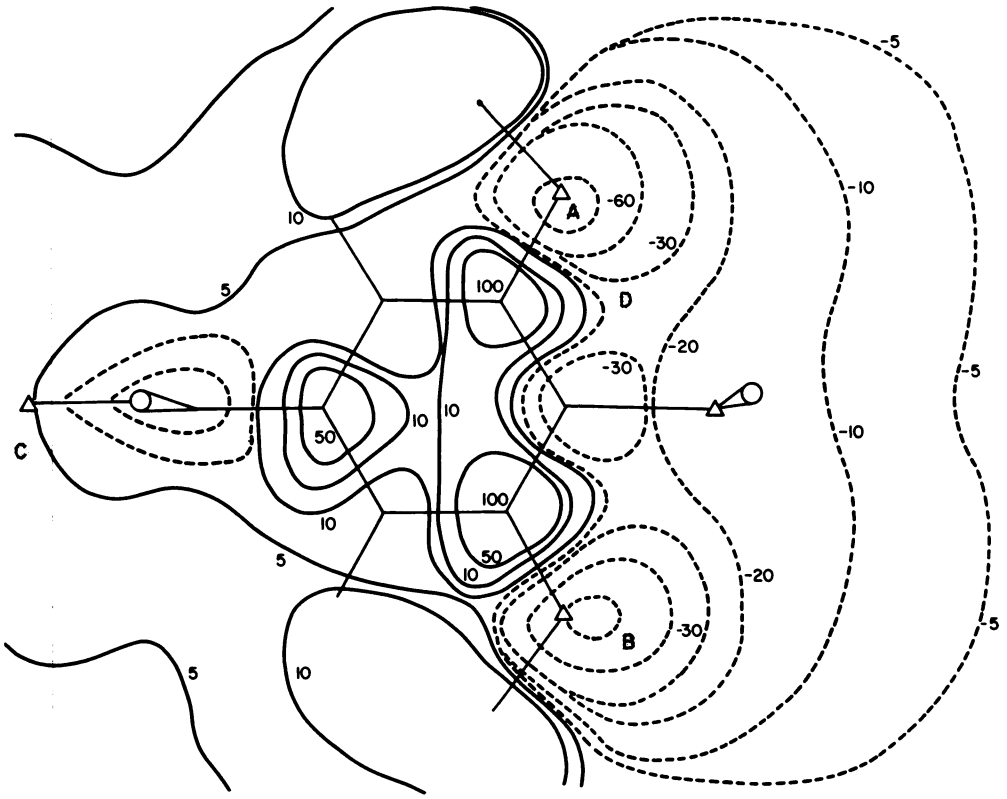

FIG. 4. IV. *Approximate electrostatic potential for 3,5-dimethoxy-4-methylthiophenethylamine in kcal/mol*

polar moiety diminishes lipophilicity as suggested by Barfknecht *et al.* (34), who have shown a modest correlation between lipophilicity and hallucinogenic activity. We believe a receptor phenomenon to be an equally plausible hypothesis, although a passive-diffusion-type mechanism cannot be discounted. In general, our work tends to coincide with the findings of other workers indicating the importance of the 3 and 4 positions in the

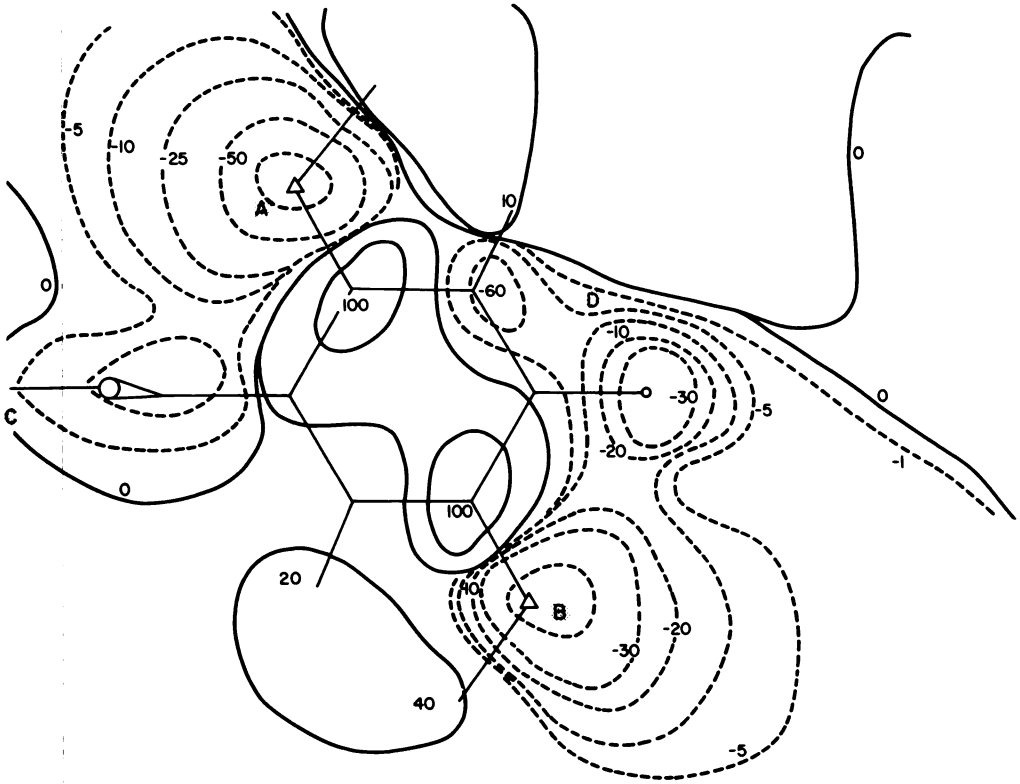

FIG. 5. V. *Approximate electrostatic potential for 2,5-dimethoxy-4-methyphenethylamine in kcal/mol*

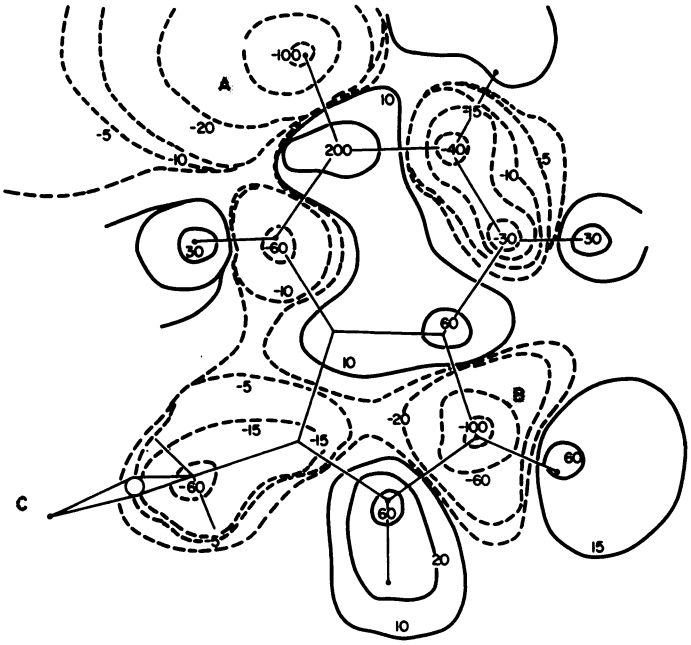

FIG. 6. VI. *Approximate electrostatic potential for serotonin in kcal/mol*

substitution pattern of the phenethylamines and their possible receptor equivalence with 5-HT.

We conclude, with some mild surprise, that a very simple model using point charges can stimulate reasonable conclusions concerning electrostatic regions at 1 to 4 Å from molecules of large size, especially when kept within the context of biological data. In our recent experience with more rigorous evaluation of electrostatic potentials for small molecules (35), we note that even the Hartree–Fock orbital picture of electron density is an average "model" of the behavior of discrete charged particles for which instantaneous infinite potential regions (Fermi holes) occur. The question must concern whether a particular model is adequate to deal with a specific question; in this study it appears that even a small number of chemically modeled point charges can be of use to pose further questions and correlate existing data.

REFERENCES

1. Shulgin, A., J. Sargent and C. Naranjo. Structure activity relationships of one-ring psychotomimetics. *Nature* **221:** 537–541 (1969).
2. Glennon, R. A., S. M. Liebowitz, and G. M. Anderson. Serotonin receptor affinities of psychoactive phenalkylamine analogues. *J. Med. Chem.* **23:** 294–299 (1980).
3. Nichols, D. E., A. T. Shulgin and D. C. Dyer. Directional lipophilic character in a series of psychotomimetic phenethylamine derivatives. *Life Sci.* **21:** 596–575 (1977).
4. Foote, W., M. Sheard and G. Aghajanian. Lysergic acid diethylamide: Sensitive neuronal units in the midbrain raphe (mouse). *Nature* **222:** 567–574 (1969).
5. Wallach, M., E. Friedman and S. Gershon. Behavioral and neurochemical effects of psychotomimetic drugs in neonate chicks. *Eur. J. Pharmacol.* **17:** 259–269 (1972).
6. Dyer, D. C. Comparison of the effects of R-(−)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane (DOM), R-(−)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane and 5-hydroxytryptamine on non-innervated vascular smooth muscle. *Res. Commun. Chem. Pathol. Pharmacol.* **14:** 449–454 (1976).
7. Barfknecht, C., D. Nichols, D. Rusterholtz, J. Long, J. Englebrecht, J. Beaton, R. J. Bradley and D. C. Dyer. Potential psychotomimetics 2-amino-1,2,3,4-tetrahydronapthalene analogs. *J. Med. Chem.* **16:** 804–808 (1973).
8. Glennon, R. A., S. M. Liebowitz and E. C. Mack. Serotonin receptor binding affinities of several hallucinogenic phenalkylamines and N,N-dimethyltryptamine analogs. *J. Med. Chem.* **21:** 822–825 (1978).
9. Kang, S., C. L. Johnson and J. P. Green. Theoretical studies on the conformations of psilocin and mescaline. *Mol. Pharmacol.* **9:** 640–648 (1973).
10. Bonaccorsi, R., E. Scrocco and J. Thomasi. Molecular SCF calculations for the ground state of some three-membered ring molecules. *J. Chem. Phys.* **52:** 5270–5281 (1970).
11. Srebrenik, S., H. Weinstein and R. Paunz. Analytic calculation of atomic and molecular electrostatic potentials from the Poisson equation. *Chem. Phys. Lett.* **20:** 419–423 (1973).
12. Weinstein, H. and R. Osman. Models for molecular mechanisms in drug receptor interactions. Serotonin and 5-hydroxyindole complexes with imidazolum cation. *Int. J. Quant. Chem.* **QBS4:** 253–268 (1977).
13. Rein, R., T. J. Swissler, V. Renugopalkrishnan and G. R. Pack. *Conformation of Biological Molecules* (E. D. Bergmann and B. Pullman, eds.). Israel Acad. Sci. Human, Jerusalem, 761–780 (1972).
14. Kier, L. B. and H. E. Aldrich. A theoretical study of receptor site models for trimethylammonium group interaction. *J. Theor. Biol.* **46:** 521–527 (1974).
15. Bonaccorsi, R., A. Pullman, E. Scrocco and J. Tomasi. N vs. O proton affinities of the amide group. Ab initio electrostatic molecular potentials. *Chem. Phys. Lett.* **12:** 622–625 (1972).
16. Politzer, P. and K. C. Daiker. A comparative analysis of the electrostatic potentials of some polycyclic aromatic hydrocarbons. *Int. J. Quant. Chem. QBS4:* 317–323 (1977).
17. Breon, T. L., H. Peterson and A. N. Peruta. Three dimensional molecular illustrations. II. Isoelectrostatic energy contour spheres of influence applied to narcotic molecules. *J. Pharm. Sci.* **67:** 73–80 (1973).
18. Kaufman, J. and W. S. Koski. Physicochemical, quantum chemical and other theoretical techniques for the understanding of the mechanism of action of CNS agents: Phychoactive drugs, narcotics narcotic antagonists and anesthetics, in *Drug Design, Vol. V* (E. J. Ariens, ed.). Academic Press, New York, 251–340 (1975).
19. Scrocco, E. and J. Tomasi. Electronic molecular structure, reactivity and intermolecular forces: An heuristic interpretation by means of electrostatic molecular potentials. *Advan. Quant. Chem.* **11:** 116–193 (1978).
20. Giessner-Prettre, C. and A. Pullman. Molecular electrostatic potential comparison of ab initio and CNDO results. *Theor. Chim. Acta* **25:** 83–88 (1972).
21. Oie, T., G. Maggiora and R. Christoffersen. Ab initio calculations on large molecules using molecular fragments: Comparison of charge distribution and molecular electrostatic potentials for ethyl chlorophyllide a and related molecules. *Int. J. Quant. Chem. QBS3:* 119–133 (1976).
22. Löwdin, P. O. On the non-orthogonality problem connected with the use of atomic wave functions in the theory of molecules and crystals. *J. Chem. Phys.* **18:** 365–375 (1950).
23. Shillady, D. D., J. F. Bloor and F. P. Billingsley. Valence shell calculations on polyatomic molecules. IV. Effect of deorthogonalization on CNDO2 dipole moments and charge distribution. *Theor. Chim. Acta* **21:** 1–8 (1971).
24. Mulliken, R. S. Electronic population analysis on LCAO-MO molecular wave functions. *J. Chem. Phys.* **23:** 1833–1840 (1955).
25. Bergin, R. *Molecular Structure of Sympathomimetic Amines and Related Substances.* Tryckeri Balder, Stockholm, 14–18 (1971).
26. Martin, M., R. Carbo, C. Petrongalo and J. Tomasi. Structure-activity relationships in phenethylamine. A comparison of quantum mechanical SCF ab initio and semiempirical calculations. *J. Amer. Chem. Soc.* **97:** 1338–1346 (1975).
27. Abrahams, S. The stereochemistry of sub-group VI B of the periodic table. *Quart. Rev.* **19:** 407–436 (1956).
28. Anderson, G., P. Kollman, L. Dommelsmith and K. Houk. Methoxy group non-planarity in ortho-dimethoxybenzenes: Simple predictive models for conformation and rotational barriers in alkoxy aromatics. *J. Amer. Chem. Soc.* **101:** 2344–2352.
29. Shulgin, A. T. and M. R. Carter. Centrally active phenethylamines. *Psychopharm. Commun.* **1:** 93–97 (1975).
30. Kier, L. B. Preferred conformation of serotonin and a postulate on the nature of its receptor from M.O. calculations. *J. Pharm. Sci.* **57:** 1188–1193 (1968).
31. Kelley, J. M. and R. H. Adamson. A comparison of common interatomic distances in serotonin and some hallucinogenic drugs. *Pharmacology* **19:** 28–31 (1973).
32. DiPaolo, T., L. H. Hall and L. B. Kier. Structure-activity studies on amphetamines using model interaction calculations. *J. Theor. Biol.* **71:** 295–303 (1978).
33. Nichols, D. E., W. R. Pfister and G. K. Yim. LSD and phenethylamine hallucinogens: New structural analogy and implications for receptor geometry. *Life Sci.* **22:** 2165–2169 (1978).
34. Barfknecht, C. F., D. E. Nichols and W. J. Dunn. Correlation of psychotomimetic activity of phenethylamines with 1-octanol-water partition coefficients. *J. Med. Chem.* **18:** 208–210 (1975).
35. Shillady, D. D. and S. Baldwin-Boisclair. Dipole-optimized Gaussian orbitals for rapid computation of electrostatic molecular potential contour maps. *Int. J. Quant. Chem. Quant. Biol. Symp.* **6:** 105–114 (1979).

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