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Reactivity Characteristics of Large Molecules and Their Biological Activity: Indolealkylamines on the LSD/Serotonin Receptor

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Abstract

Theoretical quantum mechanical methods for the characterization of molecular reactivity are applied to a series of hydroxy substituted indolealkylamines. A correlation is sought between the reactivity characteristics of these molecules and their biological activity on the LSD/serotonin receptor. The calculations are based on *ab initio* LCAO-SCF-MO wave functions. For the analysis of the early stages of drug–receptor interaction, the electrostatic potential fields calculated for the various congeners are compared to the field generated by the most active compound: 5-hydroxytryptamine. A model for the comparative orientation of the active molecules in the series is obtained on the basis of a requirement for matching electrostatic interaction fields. This requirement can be translated into observed differences in the affinity of the molecules for the biological receptor. The hypotheses for subsequent interactions with the receptor at shorter distances are analyzed in terms of the comparative ability of the molecules to interact in polarization-type complexes. The analysis focuses on the different localization of the most active sites in the various molecules. The largest single-orbital contribution to a polarization term E_2 in a perturbation expansion of the interaction between the molecule and an attacking charge is shown to come from the highest occupied molecular orbital (HOMO). This illustrates the relation between the well established frontier density criteria for reactivity and a perturbation representation of the interaction. The localization of HOMO density is found to match the sites at which the highest percentile contribution to the polarization is calculated. These findings provide a theoretical background for previously obtained correlations between biological activity and electronic structure and answer some of the questions raised by correlations with charges on atoms and frontier densities. All the findings are in excellent qualitative agreement with the biological data on the specific binding of hydroxy substituted indolealkylamines to the LSD receptor, and with data on the pharmacological activity of these compounds.

Introduction

The assumption that some sites of action of LSD and the indolealkylamines could coincide both in the CNS and on peripheral serotonergic systems is supported by pharmacological, electrophysiological, and direct receptor-binding data (see references in [1]). The search for molecular structural factors that are responsible for the action of the indolealkylamines and LSD on common receptors has therefore received considerable attention. Some structure-activity studies have focused primarily on the geometrical congruencies in the molecular structure of indolealkylamines and LSD [2–5], based on data from x-ray crystallography [4, 6] and conclusions from a variety of quantum mechanical calculations [7–9]. The hypotheses on the mechanism of action of these drugs

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are related to the early findings on the ability of the indole portion, which is a common structural element in all these molecules, to form molecular complexes of the "charge transfer" type (for a recent review see [10]). A considerable effort has therefore been made to elucidate the relation between the electronic structure of these molecules and their biological effects. The attempts to correlate indices representing the biological activity of indolealkylamines and LSD with indices representing their molecular properties derived from quantum chemical calculations, have been reviewed recently [1]. As expected, the best correlation with theoretical indices seems to involve those which are related to the ability of the molecules to form molecular "charge transfer" complexes. The general conclusions, however, do not yield a specific and generalized model for the drug–receptor complex. Thus a correlation of biological effectiveness with the energy of the highest occupied molecular orbital (HOMO) was not obtained [1], and the correlation with atomic charges and frontier densities, although much more impressive, left open some important questions concerning the mechanism and sites of drug–receptor interactions [11, 12].

An important shortcoming of most correlation approaches of this type has been the lack of a rigorous theoretical basis for the choice of the molecular reactivity indices used in the correlation. For example, although the HOMO energy is intuitively related to the "electron-donating" ability of a molecule by considerations such as Koopman's theorem, it provides a very crude reactivity index if the specific interaction between the drug and its receptor is localized in particular regions of the molecule and does not resemble an ionization process. Such a localized "electron-donating" ability would be closer to the local polarizability than to the total ionization potential. It is therefore preferable to use indices that are closely related to the physical mechanism assumed for the interaction. This is the basis for attempts to correlate the superdelocalizability indices derived from the HMO method to molecular complexation [13] and Mulliken charge and frontier electron distributions from CNDO and INDO calculations [12] with activity on isolated tissue. The most significant shortcomings of these approaches are related to the very approximate nature of the molecular orbital methods from which the indices were obtained and to the basic inaccuracy inherent in an attempt to describe the effects of interactions on the continuous electronic density function by sample points calculated according to an approximation scheme (that is, the point charges in the Mulliken population analysis). Some interesting correlations between molecular structure and biological activity were nevertheless obtained for a large number of related compounds, and the geometrical congruency considerations and indices based on the electronic structure have been used successfully to predict the activity of a different series of drugs [5, 14].

With the recently acquired capability to apply more accurate computational methods to the same molecular systems, it now becomes possible to formulate a more direct link between the electronic structure of the active compounds and the proposed mechanisms of interaction with their receptors. Based on results from *ab initio* LCAO-SCF-MO calculations, we present here a comparative analysis of reactivity characteristics of indolealkylamines which reflect their ability to generate the polarization type complexes suggested for their interaction at the receptor.

Correlations between theoretically calculated reactivity criteria and biological activity are fraught with the danger that the chemical behavior of the drugs might change in the biological environment and that subtle effects might be lost in crude biological tests of the models. Since the calculations are performed on isolated molecules and solvent effects are not taken into account, it is encouraging to find that some of the theoretical results presented here are qualitatively supported by in vitro measurements of electronic char-

acteristics and interaction patterns of the molecules by nuclear magnetic resonance and fluorescence spectroscopy [28, 29, 41] as well as by tests of biological activity [12, 31-33].

Methods

The molecular wave functions for all the calculations reported here were obtained from *ab initio* LCAO-SCF-MO computations using the POLYATOM* program. The atomic basis consists of five *s*- and three *p*-type Gaussian functions on the heavy atoms and two *s*-type Gaussians on the hydrogens, contracted to a minimal basis. The exponents for the (5*s*,3*p*,2*s*/2*s*,*p*,*s*) basis are the optimized values from Whitman and Hornback [15]. The molecular electrostatic potential is calculated from the molecular wave functions by a method described in detail elsewhere [16]. The electrostatic potentials have been shown to be directly measurable experimentally [17], and their use as reactivity criteria has been reviewed recently [18]. In the figures presented in this paper the electrostatic potential maps are represented numerically in terms of the interaction energy with a positive point charge and expressed in kcal/mole. The electrostatic interaction energy is the first term in a perturbation expansion of the interaction between the molecule and an external point charge q, which generates a perturbing field $w = q/|\bar{r} - \bar{r}_q|$. The form of some subsequent terms in the perturbation expansion has been given in [19]. Within the uncoupled Hartree-Fock approximation, the second-order term E_2($E_{2,0}$ in the double perturbation of [19]) is obtained as

$$E_2 = 2\sum_i \langle i^{(1)} | w | i^{(0)} \rangle = 2\sum_i^{\text{occ}} \sum_p^{\text{unocc}} \frac{|\langle p^{(0)} | w | i^{(0)} \rangle|^2}{\epsilon_i^{(0)} - \epsilon_p^{(0)}} \tag{1}$$

where $i^{(0)}$ and $p^{(0)}$ represent occupied and unoccupied molecular orbitals of the unperturbed molecule and $\epsilon_i^{(0)}$ and $\epsilon_p^{(0)}$ are the corresponding orbital energies. For a point-charge system, the E_2 term in Equation (1) is equivalent to the induction contribution E_I in the derivations of Murrell and coworkers [20-22] and includes the polarization response of the molecule to the perturbation caused by the attacking species [19].

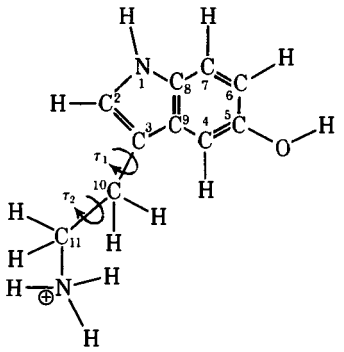
All calculations were performed with the tryptamine derivatives in the Falkenberg averaged geometry [23] with the side chain in the least interfering, fully extended conformation ($\tau_1 = 90°$, $\tau_2 = 180°$) which also corresponds to the geometry in solution (for a review see [9]).

The reactivity characteristics of the molecules (such as potential and polarization maps, HOMO localization) were studied in planes parallel to the indole ring system and situated at distances of 1.9 a.u. (1 Å) and 3 a.u. (1.6 Å) from the molecular plane. The plane cutting through the electron distribution at the shorter distance (1.9 a.u.) was chosen to reflect mainly contributions from the π-electron density, whereas the distance chosen for the representation of reactivity characteristics (3 a.u.) is approximately half the separation between atoms achieving "close contact" in crystals of molecular polarization or charge transfer complexes of these molecules [24]. This choice of planes enables us to study the interaction of the fields generated by the indolealkylamines with the electron distribution of their counterparts in the polarization complex. The nuclei of the molecules in the complex remain separated by at least the crystallographic "close contact" distance of 3.3 Å.

The molecules studied here were tryptamine (TRYP), 4-hydroxytryptamine (4-HT),

* The POLYATOM program package was obtained from the Quantum Chemistry Program Exchange (QCPE #238), Indiana University.

5-hydroxytryptamine (5-HT, serotonin), 6-hydroxytryptamine (6-HT), and 7-hydroxytryptamine (7-HT). The atom numbering system is defined in Scheme I.



Scheme I.

All the maps presented in this work were drawn with the aid of the PROPHET computer system which is a specialized computer resource developed by the Chemical/Biological Information-Handling Program of the National Institutes of Health [40].

Results and Discussion

It has been shown for a variety of systems that the early stages of drug–receptor recognition can be characterized by requirements for matching molecular interaction potentials between the drug and the unknown receptor [25, 26]. At this early stage the

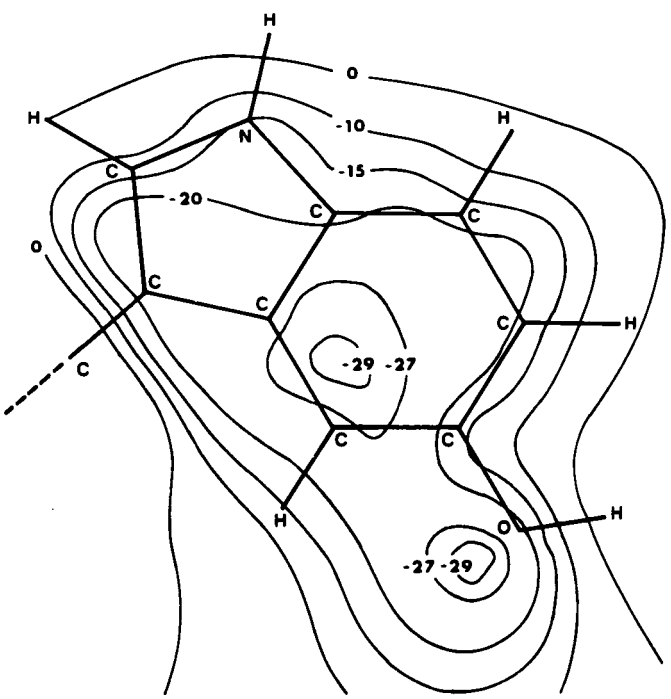
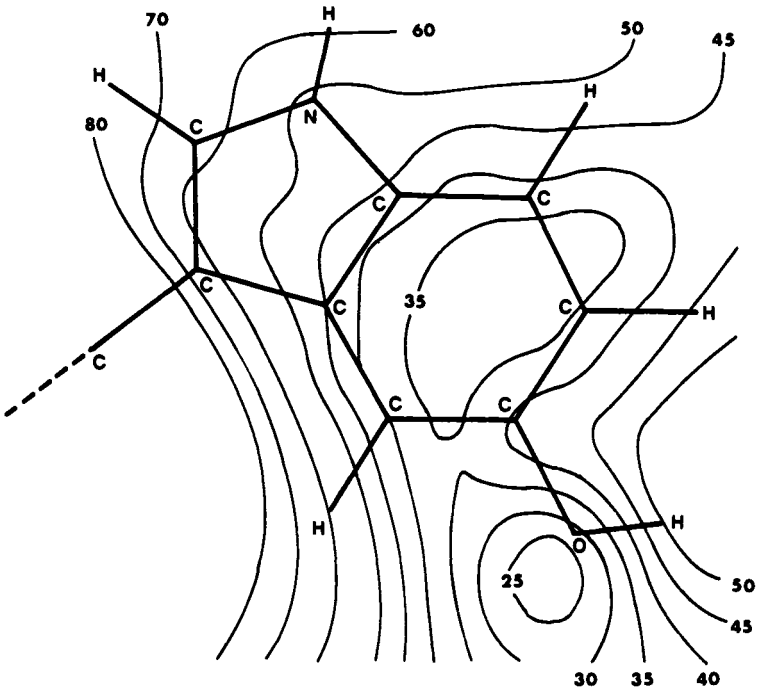
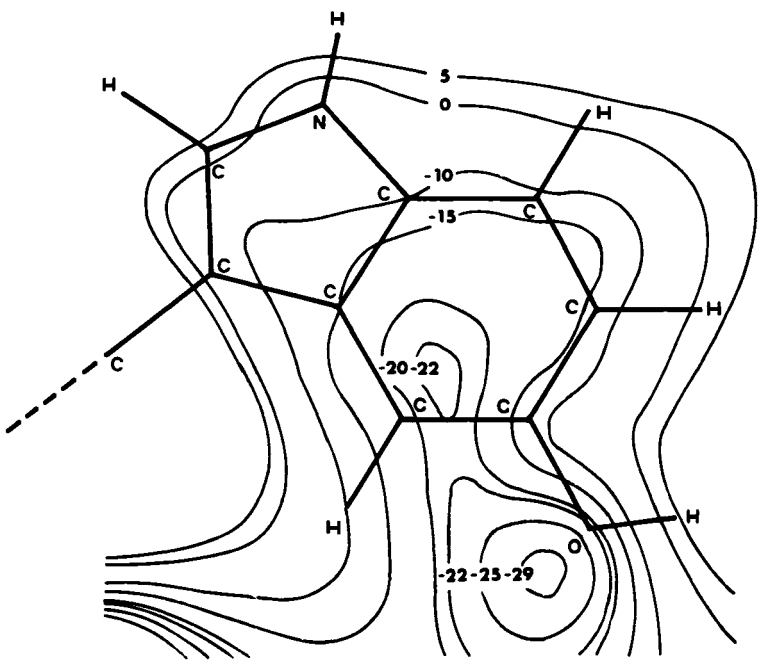


Figure 1. Electrostatic potential map in a plane 1.6 Å above the indole system of neutral 5-hydroxytryptamine (5-HT). Values are in kcal/mole. See Methods for details and atom numbering scheme.



(a)



(b)

Figure 2. Electrostatic potential maps (a) 5-HT monocation, (b) supermolecular system of 5-HT interacting with OH^-. Details as in Figure 1.

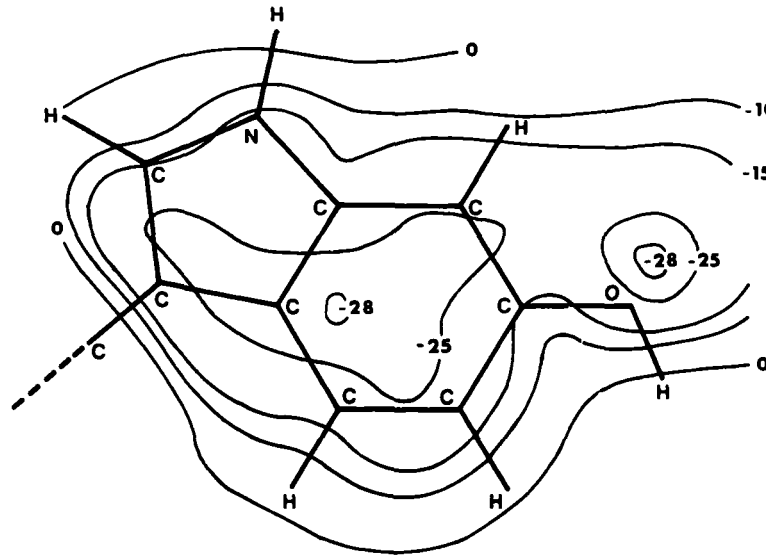


Figure 3. Electrostatic potential map for neutral 6-HT. See Figure 1 and Methods for details.

criteria for drug-receptor complementarity are translated into matching patterns of the electrostatic potential fields generated by the interacting molecules—the interaction pharmacophore [27]. When this pattern is established for a known active compound, the ability of other molecules to interact with the same receptor is predicted on the basis of their ability to generate a similar interaction pharmacophore. The possibility that these basic reactivity criteria may relate to the potency of the indolealkylamines studied here has therefore been investigated first. Figure 1 shows the electrostatic potential generated by 5-HT in a plane parallel to the indole portion, at 3 a.u. (1.6 Å) above it (see the Section Methods for the choice of plane). The electrostatic potential in Figure 1 is calculated for the free-base form even though at physiological pH these molecules would be mostly in the cationic form, protonated at the side-chain amine. The reason for our interest in the neutralized species is based on the considerable amount of evidence that shows the

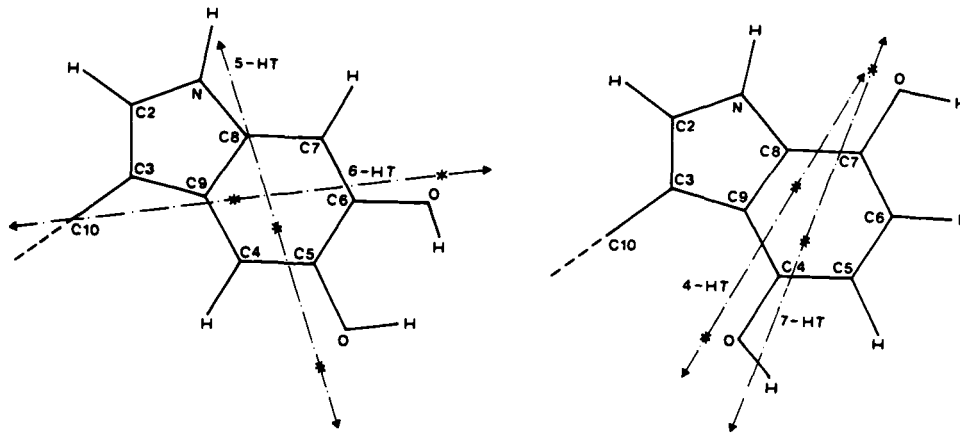


Figure 4. Molecular orientation vectors for optimal electrostatic interaction of the indole system in 5-HT, 4-HT, 7-HT, and 6-HT. See text for details.

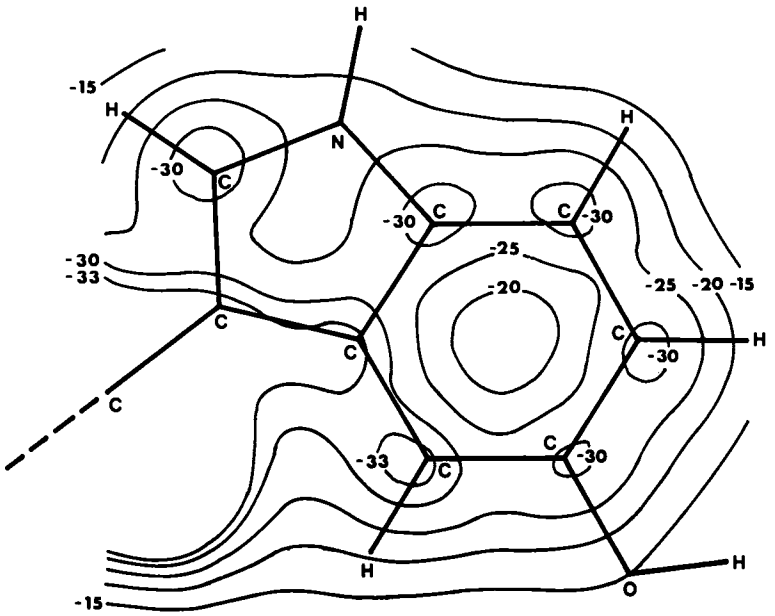
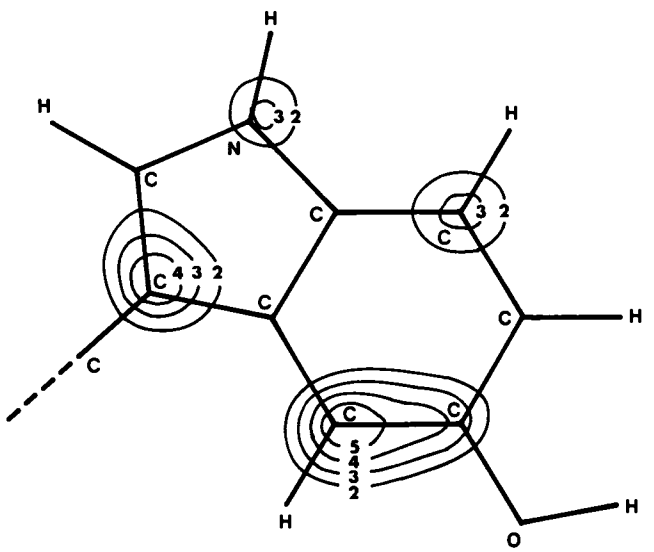


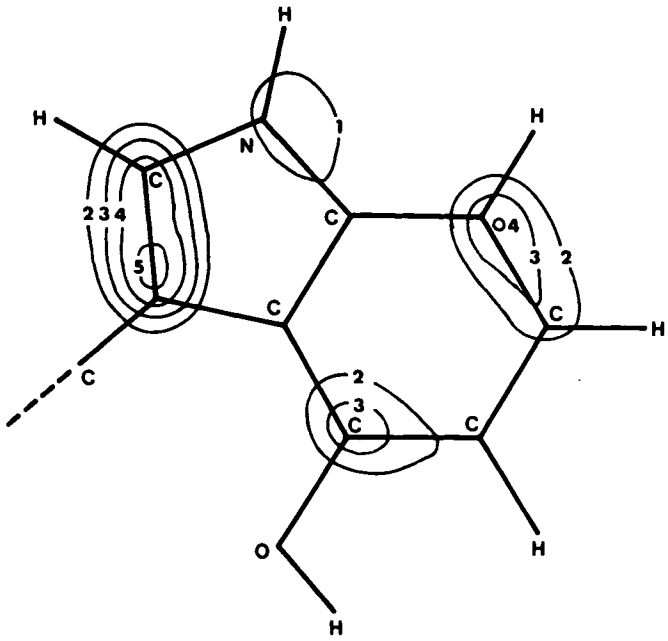
Figure 5. Mapping of E_2 (polarization term) values for neutral 5-HT. See Figure 1 and text for details.

cationic head of indolealkylamines to be directly involved in interactions with anionic groups of biological molecules in in vitro solutions [28, 29] and, most probably, with an anionic site of receptors [1]. We have shown for other series of drugs that the results of such interaction with anionic sites is to confer on the electronic structures of the molecules all the major characteristics of the neutral species [25, 27, 30]. The validity of this observation has been verified here for 5-HT. The comparison of the potential generated



(a)

Fig. 6 (*continued*)



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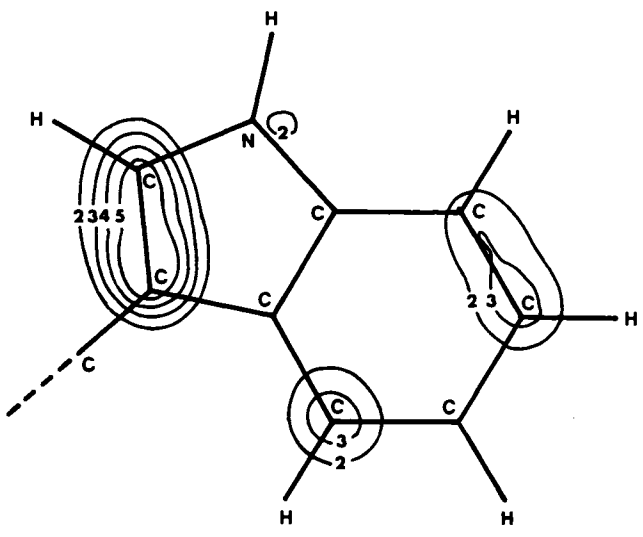
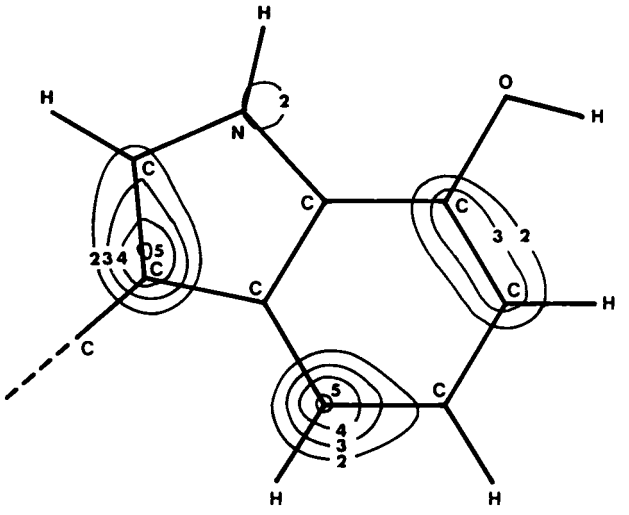


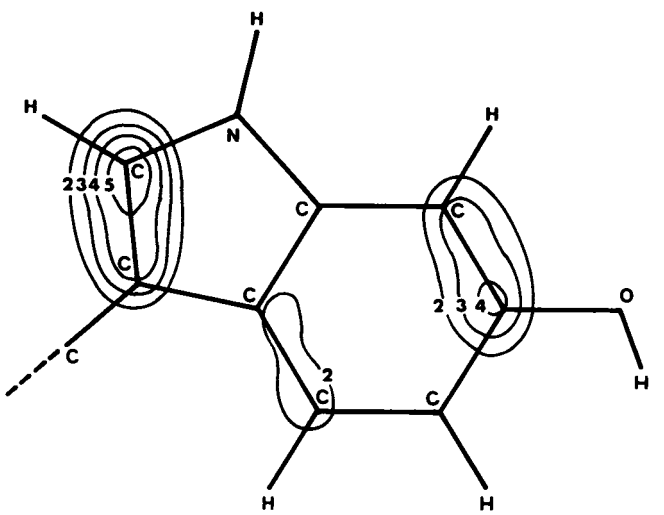
(c)

Fig. 6 (*continued*)

by 5-HT monocation with the potential generated by 5-HT interacting with the model of a negative site (OH-) is shown in Figure 2. Following the interaction, the potential above the indole portion changes from totally positive (that is, repulsive to a positive species) in 5-HT monocation to totally negative (that is, attractive to a positive charge) in the neutralized complex. Moreover, Figure 2(b) is identical in its characteristics (shape of contours, size, and position of minima) to the potential generated by 5-HT free base shown in Figure 1. Since the interaction of the cationic head with a matching negative



(d)



(e)

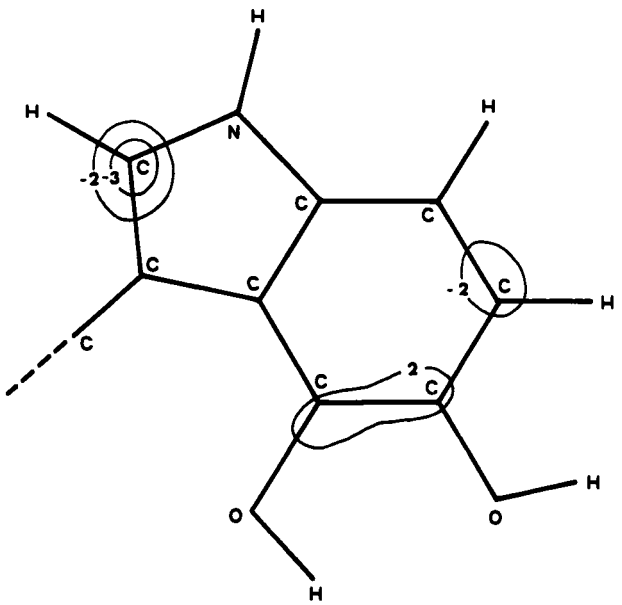
Figure 6. Maps of electron density distribution from the highest occupied molecular orbital (HOMO) in a plane 1 Å above the indole ring system. Contour values are $n \times 10^{-3}$ electrons/a.u.^{3}. (a) 5-HT, (b) 4-HT, (c) TRYP, (d) 7-HT, (e) 6-HT.

site in the receptor is assumed to be the primary event (it will clearly be the main term in an energetical consideration), it becomes necessary to study the neutralized molecule for the elucidation of the secondary interaction with the receptor, in which the indole portion will be involved.

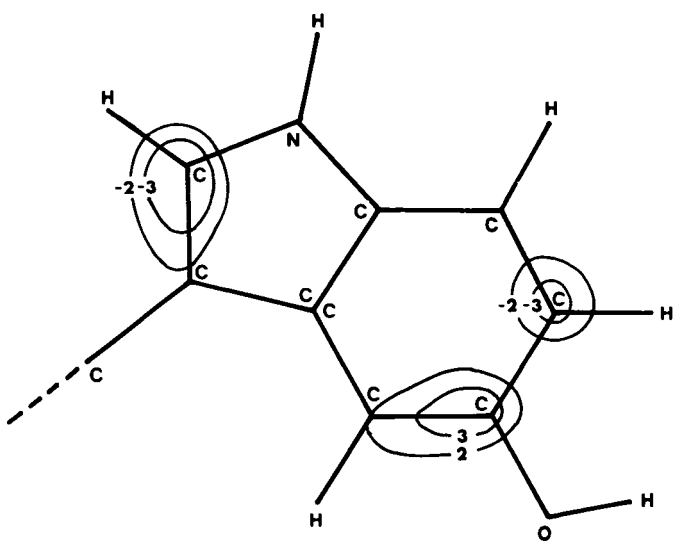
Figure 3 shows the electrostatic potential calculated for neutral 6-HT in the same plane as Figure 1. 5-HT and 6-HT have been found to be the most active and the least active members, respectively, in the series of monohydroxy substituted indolealkylamines studied in biological tests in which specific binding to biological material [31, 32] and activation

of serotonergic receptors [12, 33] were measured. It is therefore interesting to focus on the differences in the electrostatic reactivity characteristics of 5-HT and 6-HT and to compare them to those of compounds with intermediate activity.

Since the direction of the derivative of the potential field generated by the molecule at each point gives the direction of the force applied by the molecular charge distribution on point charges in the surroundings ($\overline{\nabla}v = \overline{F}$), it is possible to infer on the orientation of the molecule relative to a polar group in the receptor from the alignment of the regions of the most negative potential. The vectors in Figure 4 connect the most negative regions



(a)



(b)

Fig. 7 (*continued*)

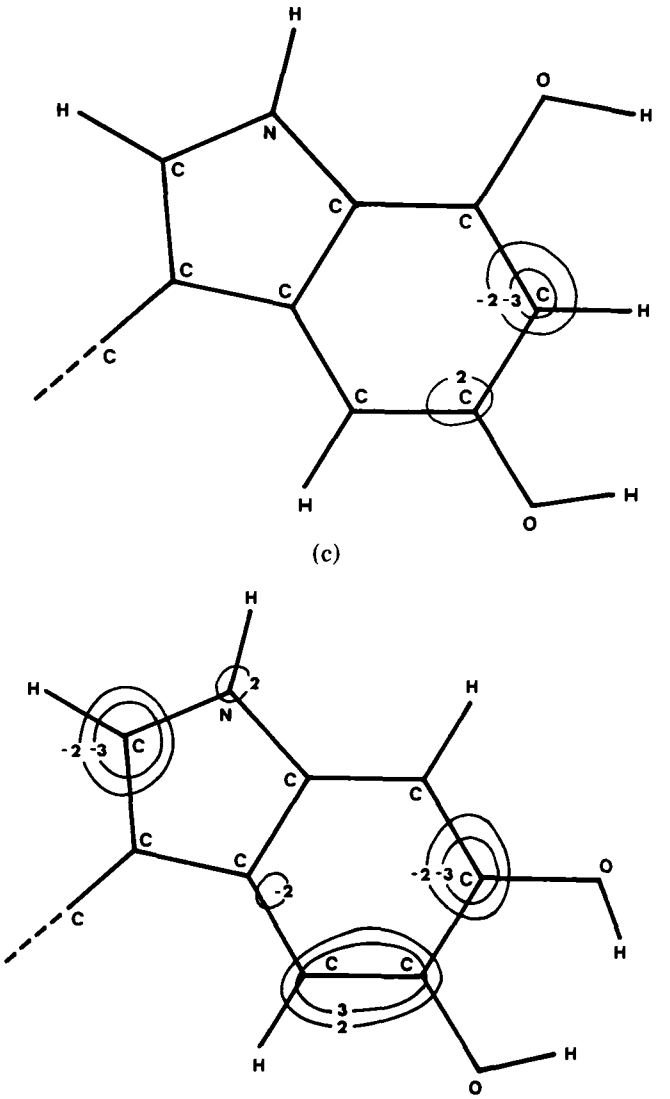


Figure 7. HOMO-electron density difference maps. The electron distribution is from the HOMO of (a) 5-HT minus 4-HT; (b) 5-HT minus TRYP; (c) 5-HT minus 7-HT; (d) 5-HT minus 6-HT. Both positive contours (higher 5-HT HOMO density) and negative contours are shown. Values are $n \times 10^{-3}$ electrons/a.u.[3]

(potential minima) in the molecular electrostatic potential map of the hydroxy-indolealkylamines studied, such as the −29-kcal/mole regions near C4 and the hydroxyl oxygen of 5-HT in Figure 1. The location of the minimum generated by the hydroxyl group, which is a key factor in the determination of the vectors, depends on the rotation angle around the C-OH axis and will finally depend on the mutual adaptation of drug and receptor. It is, however, clear from inspection that whatever the resulting geometry may be, the vectors in 5-HT, 4-HT, and 7-HT (Fig. 4) will have the general orientation of an axis between the C4-C5 bond and the C8-C7 bond. The vector in 6-HT (Fig. 4) is approximately perpendicular to that direction. It then follows that in the early stages

of interaction, when the cationic head of the side chain is already interacting with a negative site, the electrostatic force will favor an orientation of the ring system of 6-HT relative to the receptor which is different from the one favored for 5-HT. However, if steric considerations and proximal atom-to-atom interactions favor a similar approach for both 5-HT and 6-HT at shorter distances from the receptor, the 5-HT-like orientation of 6-HT would be achieved at the expense of conformational energy. For the drug–receptor interaction this energy expenditure should be expressed as a reduced receptor-binding probability of 6-HT compared to 5-HT. The considerable difference between the orientation vectors of 5-HT and 6-HT and the similarity in the directions of the vectors in 4-HT and TRYP correlate well with the measured affinity of these compounds to the LSD receptor (5-HT $\gg$ 4-HT $\geqslant$ TRYP $\geqslant$ 7-HT $\gg$ 6-HT) [31, 32] as well as with their potency in contracting rat stomach muscle (5-HT $\gg$ 4-HT $\geqslant$ TRYP $>$ 7-OCH_3T $\gg$ 6-HT) [12, 33].

While the characteristics of the electrostatic interaction of the molecules might provide an indication of the forces involved in a fitting orientation of drug and receptor in the preliminary stages, it is important to follow the effects of the subsequent interactions on the reactivity. Since we are considering the basic hypothesis of polarization complexes between drug and receptor, we shall focus on theoretical formulations which are reflective of the degree of interaction (reactivity) of the drugs in this type of system. A first-order indication is given by the polarizability term in the interaction of the system with an external point-charge perturbation. A detailed theoretical description of this term ($E_{2,0}$ in a double perturbation, E_2 when only one perturbing species is involved) has been given elsewhere [19], where it is shown that its physical significance is related to the polarization response of the system to the external perturbation. The larger the absolute value of this term, the stronger the electronic charge distribution of the molecule will be affected by the external perturbation. A complete mapping of the values of this polarization term in the space surrounding the molecule should therefore indicate the regions that are most susceptible to polarization by external agents. Figure 5 shows such a map for 5-HT in the same plane used for the description of the electrostatic potential. The fused ring region (above C8 and C9) is obviously the most polarizable in the entire indole system. These results provide a strong indication that the bridge region will play an important role in the stabilization of any polarization-type complex that is based on the "electron-donating" capabilities of the indolealkylamines. The close contacts with electrophilic centers observed for the C8 and C9 bridge atoms in the crystal structures of the serotonin–picrate monohydrate and serotonin–creatinin sulphate complexes confirm these theoretical findings [24, 34].

Following the hypothesis of drug–receptor complexes of the electron donor–acceptor type, the comparative compatibility of the drugs in this indolealkylamine series with the biological receptor also depends on the localization of the sites in the molecule that are susceptible to polarization interactions. The question arises whether such sites exist in all congeners and how their distribution matches the pattern set by the most active compound in the series. We have therefore investigated the elements of the electronic structure that are related to the specific localization of the reactive sites in polarization interactions.

An important conceptual tool in the characterization of chemical reactions that are not "charge controlled" is the "frontier density." The definition of "frontier-controlled" reactions is well documented [35, 36] and relates the initial sites of attack of a molecule by an electrophile to the localization of the highest electron density in the HOMO (see also [37]). Figure 6 shows a comparison of the localization of this orbital in 5-HT, 4-HT,

TABLE I. Contribution of HOMO to the total polarization term E_2.[a]

Position Above Atom	5 - HT	4 - HT	Tryptamine	7 - HT	6 - HT
C2	-4.2(10%)	-11.3(28%)	-12.3(35%)	-7.3(18%)	-14.0(35%)
C4	-13.0(31%)	-9.6(24%)	-9.6(27%)	-12.4(30%)	-8.0(20%)
C5	-9.1(24%)	-6.5(17%)	-5.0(15%)	-7.2(19%)	-4.7(12%)
C6	-3.3(9%)	-8.8(23%)	-9.4(27%)	-9.3(24%)	-10.6(28%)
C7	-7.6(20%)	-8.5(22%)	-6.5(18%)	-7.6(20%)	-7.8(20%)
N1	-7.6(27%)	-6.6(24%)	-6.7(22%)	-7.1(25%)	-6.2(22%)
C8	-2.6(7%)	-2.9(7%)	-3.1(7%)	-1.5(4%)	-5.0(13%)
C9	-4.1(10%)	-2.9(7%)	-2.7(7%)	-2.8(7%)	-4.3(11%)

[a] E_2 (HOMO) values are in kcal/mole calculated at a distance of 3 a.u. above the corresponding atoms. Numbers in parentheses represent the percentage of the contribution from HOMO to the total value of E_2 calculated at the same point from the total molecular wave function.

tryptamine, 7-HT, and 6-HT in the same plane used in Figure 1. The remarkable resemblance between the localzzation patterns of the HOMO in 4-HT, 7-HT, and tryptamine, and the fact that the HOMO density in these molecules seems to be intermediate between the localization of 5-HT and that of 6-HT, correlate well with the biological data on the series. The differences in localization of HOMO densities are given in Figure 7, which shows that the difference between 5-HT and 4-HT, 7-HT, or tryptamine is much smaller than the difference between the 5-HT and the 6-HT HOMO. Moreover, the HOMO of the most potent compound (5-HT) has higher density than that of the least potent congener (6-HT) in exactly the same regions that were singled out by the potential and polarization maps as being the most important for binding to the receptor (that is, C4-C5). The significance of an interaction at N1 for the activation of the C8 site as an "electron donor" is related to the function of nitrogen as a "charge transformer" [38, 39] and will be discussed elsewhere.

The ability to calculate a perturbation term that is proportional to the polarization response of the molecular system to an attacking agent (the E_2 term) allows us to study the relation between criteria based on HOMO localization and components of the reactivity calculation. It is therefore interesting to assess whether the contribution from HOMO to the total E_2 term is of major significance. Table I shows that HOMO has a disproportionately large contribution to the total value of $E_{2,0}$: although it is only one of 47 occupied orbitals in the hydroxytryptamines (~2 percent), it contributes more than 30 percent of the total E_2 value on C4 and well over 20 percent on the C5 and N1 atoms of 5-HT. It is also evident that in all the molecules of the series, the largest contributions from HOMO to E_2 appear on centers with the highest HOMO electron density (compare Table I and Fig. 6). This finding establishes a relation between the localization of HOMOs and the most reactive sites in a reaction that depends heavily on electron affinity and polarization. The general applicability of this conclusion is suggested by the fact that the relation is observed in all congeners studied, although their HOMOs are localized on different centers. This finding offers theoretical support for the use of reactivity criteria based on HOMO localization in reactions depending on the initial polarizability of the reactants. It emphasizes, however, that a correlation of reactivity with HOMO energy is to be expected in polarization complexes only if the general localization and the total

density distributed by the HOMO on the various centers are identical in all the molecules compared in the correlation. The very diverse localization characteristics we found here for the HOMO of the tryptamine congeners indicates one reason for the failure of the HOMO energy criterion in the correlation with biological activity [1].

The considerable contribution of the C4-C5 and the importance of the bridge region to the overall electrostatic reactivity pattern of the biologically active indolealkylamines explains the good correlation observed earlier between the activity and the charge and the frontier density on these atoms [11]. Moreover, the formulation of a requirement for a specific localization of HOMOs could explain why negative correlations have been obtained with the frontier density on C2, C6, and C9 [12]. This finding was considered surprising [12] because it seemed to contradict the relation between activity and electron-donating ability. However, a comparison of Figure 6(a) and (e) and of Figure 7(a) and (d) suggests that high HOMO densities on the C4-C5 and N1-C8 regions are obtained only at the expense of the C6-C7 and C2 regions. Therefore, if the electron-donating (high polarizability) properties of the primary indolealkylamines have to be localized in certain regions of the molecule in order to match the spatial requirements for interaction with the receptor, the correlation of biological activity with the frontier densities should be expected to be positive for certain atoms (high frontier density on C4,C5) and negative with the others (low frontier density on C2,C6).

The reactivity criteria obtained from the calculations, and in particular the effect of the hydroxyl group position on the activation of different sites in the indole ring, are in very good agreement with the experimental identification of the most reactive sites in substituted indoles as shown by nuclear magnetic resonance [41]. The experimental findings on the complexation of indolealkylamines with nucleic acids further support the mechanisms suggested from the calculations by emphasizing the importance of the ionic interaction of the side chain [28, 29], the "polarization" rather than pure "charge-transfer" nature of the ring interactions [29], and the effect of the hydroxyl substitution on the polarizability of the indole system [28]. These experimental findings illustrate the importance of intramolecular characteristics of the electronic structure in determining the reactivity properties of the molecules.

Conclusions

The calculation of electronic structure and certain types of reactivity characteristics indicates that the requirements for the interaction of 5-hydroxytryptamine and its congeners with their receptor can be represented as a spatially ordered polarization interaction pattern generated by the indole ring. This interaction of the ring portion is triggered by a primary step in which the cationic alkylamine fragment interacts with a negative site. The calculations identify the molecular fragments of the indole system that would contribute most to the polarization interaction with a receptor. The position of these reactive sites relative to the cationic head of the molecules varies in the different congeners studied. The need for a conformational adaptation of the molecules to the geometrical requirements inferred from the most active compounds would explain the differences observed in the concentrations of each molecules that are needed to obtain the same amount of drug–receptor complex. We find a very good qualitative agreement between the theoretical criteria and the experimental results measuring two different aspects of drug activity for this series: (*1*) the degree of binding of the molecules to receptors from brain tissue [31, 32], and (*2*) a specific pharmacological effect of the molecules, that is, contraction of rat stomach muscle [12, 33].

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