Theoretical Models for Molecular Mechanisms in Biological Systems: Tryptamine Congeners Acting on an LSD–Serotonin Receptor

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Abstract

Molecular reactivity criteria obtained for a congeneric series of tryptamine derivatives have led to the following hypothesis for the interaction of these molecules with an experimentally defined LSD-serotonin high-affinity binding site: the difference between the affinity of 5-hydroxytryptamine (5-HT) and that of any other congener is related to the discrepancy between the preferred electrostatic orientation of 5-HT and that of the congener in the field of the receptor. *Ab initio* LCAO-SCF calculations of complexes between 5-HT, 6-HT, 5-hydroxyindole (5-HIND), and 6-HIND with imidazolium cation, were used to test this hypothesis. For the particular configurations of the complexes presented here, the results indicate that the electrostatic orientation vectors determined from the reactivity characteristics of the molecules are good predictors of the preferred mutual orientations of the molecules in these complexes. The decomposition of the stabilization energies into electrostatic (ES), polarization (PL), exchange repulsion (EX), and "charge-transfer" (CT + mix) terms provide the basis for the possible validity of the reactivity criteria by indicating that the complexes are electrostatic in nature. The small contribution of the (CT + mix) term indicates that the main changes in electron distribution upon complex formation are in the form of charge polarization. Density-difference maps and partial integrations (in chosen planes) of the total electron density support this conclusion. These maps also indicate that the same pattern of charge redistribution is observed with all the tryptamine congeners studied, if the configuration of the complex is electrostatically equivalent to that formed between 5-HT and the common receptor site. This is in full agreement with the biological data that show that all tryptamine congeners we study here have the same intrinsic activity. The polarization complexes with imidazolium are therefore considered a useful model for further studies of the molecular mechanisms in the interaction with the LSD-serotonin binding site.

Introduction

In recent reports [1-3] we described theoretical approaches to the study of the biological activity of a congeneric series of molecules: tryptamine derivatives. The experimental data on which these studies are based exemplify a general type of problem that can be approached by studies of structure activity relationships (SAR): drugs in a congeneric series are known to have different affinities for a common site, e.g., a receptor, of unknown structure. We have reviewed the ev-

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idence for the action of the tryptamine derivatives on a common LSD-serotonin receptor (Refs. 1, 3 and references therein) and have described and compared *molecular reactivity criteria* calculated for these drugs as a possible approach to the explanation of their ability to interact with this receptor [1]. The main parameters used in these studies for the description of reactivity of 5-HT congeners with the LSD-serotonin receptor were: (a) the force vector describing the preferred alignment of the molecules in a localized electrostatic field, and (b) the localization of the density in the highest occupied molecular orbital (HOMO) of the molecules. Notably, the sites at which the electron density is localized by the HOMO, have been shown to correspond to the molecular regions that contribute most to the polarization term in a perturbation expansion of the interaction between the molecule and an attacking charged species [1]. The use of molecular reactivity parameters as predictors for biological activity is not only of immediate practical value in the design of specific drugs, but is a most important element in the elucidation of the molecular structural factors that are responsible for the biological activity of the molecules. In order to test the predictive value of the reactivity criteria, and especially in order to learn about the possible molecular and electronic mechanisms involved in the activation of the LSD-serotonin receptor by tryptamine derivatives, we have begun to construct and to analyze some model complexes that simulate the predicted reactivity and indicate the possible modes of interaction common to molecules in this series [2].

Some of the limitations of SAR studies in general and, in particular, those of the quantum-chemical approaches that apply to our studies on this congeneric series, are well known and we have discussed them previously [1,2]. Owing to the combined use of experimental and theoretical studies we were able to propose some of the elements that may represent the basic relation between the electronic structure of these drugs and their ability to bind to the receptor and elicit a response [1,3]. The main conclusions obtained thus far [1–3] regarding the possible modes of interaction of 5-HT congeners with the receptor are that: (a) the interaction of the protonated ethylamine side chain with a matching receptor site triggers the indole portion for subsequent interaction; (b) the side chain anchored at one receptor site and the force vector of 5-HT define an interaction-orientation of the molecule with the receptor; (c) in order to achieve an interaction geometry that is electrostatically equivalent to that of 5-HT, other tryptamine derivatives will have to match the interaction-orientation defined in b. This can be achieved by a conformational change in the alkylamine side chain of the congeners. If energy is needed for this reorientation, the probability for the formation of the drug-receptor complex should be lower for a congener than for 5-HT itself.

A working hypothesis emerges from these conclusions: The measured difference between the affinity of 5-HT and that of any other congener for the LSD-serotonin receptor results from the discrepancy between the optimal electrostatic orientation of 5-HT and that of the congeners. The hypothesis proposes therefore a direct relationship between the measured affinity of the congeners for the biological receptor, and the molecular structural elements that define their reactivity.

We present here the first results in a continuing series of tests of this hypothesis: the complexes of 5-HT and 6-hydroxytryptamine with imidazolium cation (IMID) are studied in the orientations that were predicted by the force vectors to be preferred energetically [1,2]. The nature of the complexes is studied and the possible implications for the biological activity of 5-HT congeners are discussed. Because 5-HT and 6-HT have been shown to have very different affinities but similar pharmacological effects on an LSD–serotonin receptor (Ref. 3, and references therein), we also examine here the possible mechanism by which the charge redistribution due to the interaction could explain the similar responses elicited by the two drugs.

Methods

The Model

Using *ab initio* and near *ab initio* methods (i.e., model potential and pseudopotential (Ref. 4, and references therein)) we have studied the electronic structures of 5-HT, 6-HT, 5-HIND, and IMID as well as the interactions in complexes of 5-HT and of 5-HIND with IMID [1,2]. The optimum electrostatic orientation vectors for some 5-HT congeners were presented schematically in Figure 4 of Ref. 1; the vector for IMID is shown in Figure 1. We begin to investigate here the relation between orientational preferences, and the electronic structures of complexes of 5-HT and 6-HT with IMID. Since we had shown previously that the electrostatic potential maps for 5-HT and 5-HIND generate identical electrostatic orientation vectors, we compare these complexes with the geometrical orientations obtained for 5-HIND and 6-HIND, respectively. The

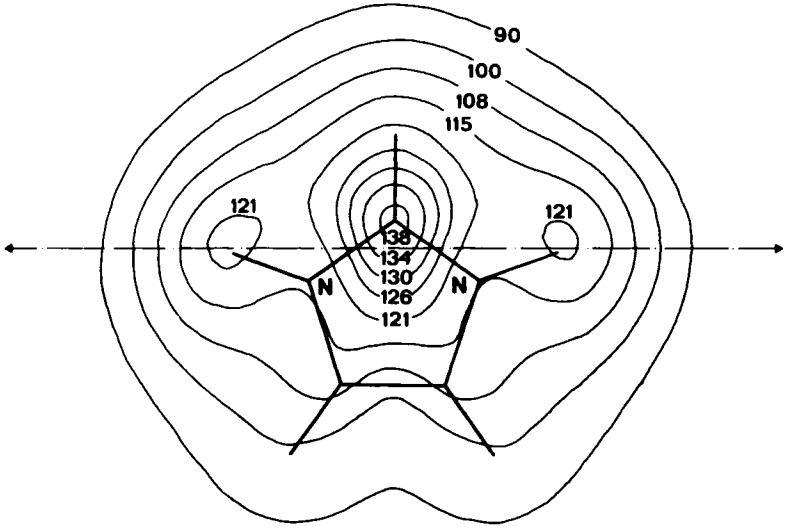


Figure 1. Molecular electrostatic potential and the electrostatic orientation vector of imidazolium cation. Contours represent the electrostatic potential in a plane parallel to IMID at a distance of 1.6 Å. Values are in kcal/mol.

position of the orientation vectors in 5-HT and 6-HT is given below with reference to the coordinate frame of 5-HT (see Table I):

$$\text{position of 5-HT vector:} \quad z = -0.59\,x + 1.25$$

$$\text{position of 6-HT vector:} \quad z = 5.08\,x - 10.37$$

In order to test the relative importance of vector alignment for the stabilization of complexes with IMID, we studied the following supermolecular systems:

(a) [5-HT + IMID] and [6-HT + IMID] in a mutual configuration that aligns the vector of IMID with that of 5-HT (to be referred to as A-5).

(b) [6-HT + IMID] and [5-HT + IMID] in a configuration that aligns the vector of IMID with that of 6-HT (referred to as A-6).

(c) The [5-HIND + IMID] complex in the A-5 and A-6 configurations.

(d) The [6-HIND + IMID] complex in the A-5 and A-6 configurations.

The equations for the IMID vector when the molecule is placed in the A-5 and A-6 configurations are:

$$\text{A-5:} \quad z = -0.610\,x - 2.302$$

$$\text{A-6:} \quad z = 5.304\,x - 7.778$$

The coordinates for IMID in the A-5 and A-6 configuration are given in Tables II and III.

TABLE I. 5-HT coordinates.

Atom	x	y	z
N 1	6.5337	0.0	-1.5405
C 2	5.5785	0.0	-3.9407
C 3	3.0092	0.0	-3.8779
C 4	0.0	0.0	0.0
C 5	0.0	0.0	2.5852
C 6	2.2558	0.0	3.9675
C 7	4.5522	0.0	2.7721
C 8	4.5660	0.0	0.1472
C 9	2.3249	0.0	-1.2695
C B	1.2625	0.0	-6.1056
C A	0.5946	2.6525	-6.9574
N AL	-1.1195	2.6670	-9.1435
HB1	-0.4739	-0.9726	-5.5747
HB2	2.1923	-0.9726	-7.6652
HA1	2.3316	3.6272	-7.4824
HA2	-0.3296	3.6272	-5.3958
H 1	8.4610	0.0	-1.1554
H 2	6.7666	0.0	-5.6002
HN1	-1.5063	4.4699	-9.6367
HN2	-2.7413	1.7706	-8.6862
H 4	-1.7675	-0.0	-1.0205
H 6	2.1668	-0.0	6.0065
H 7	6.3321	-0.0	3.7709
O 5	-2.3132	0.0	3.7894
H 5	-2.0764	0.0	5.5880

TABLE II. Coordinates of IMID in A-5 configuration.

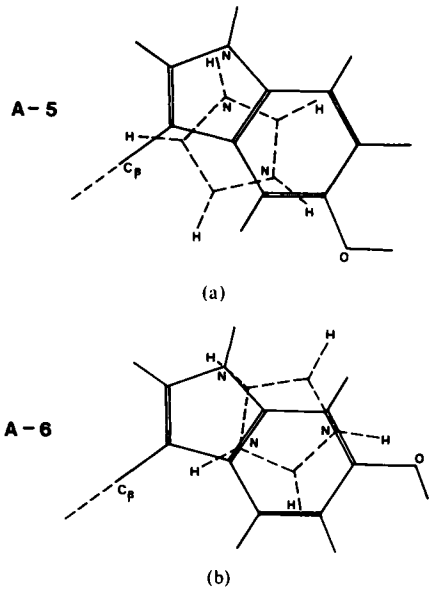
Atom	x	y	z
N1	0.7686	-6.2380	0.4502
C2	3.2928	-6.2380	0.5904
N3	4.3260	-6.2380	-1.6928
C4	2.3639	-6.2380	-3.3852
C5	0.1649	-6.2380	-2.0762
H1	-0.5155	-6.2380	1.9873
H2	4.2979	-6.2380	2.3479
H3	6.2810	-6.2380	-2.1250
H4	2.5430	-6.2380	-5.4375
H5	-1.7316	-6.2380	-2.8776

TABLE III. Coordinates of IMID in A-6 configuration.

Atom	x	y	z
N1	2.9483	-6.2380	-0.8685
C2	1.9330	-6.2380	1.4466
N3	3.7098	-6.2380	3.2140
C4	5.9822	-6.2380	1.9689
C5	5.5261	-6.2380	-0.5493
H1	1.9583	-6.2380	-2.6097
H2	-0.0651	-6.2380	1.7726
H3	3.4299	-6.2380	5.1966
H4	7.8417	-6.2380	2.8553
H5	6.9410	-6.2380	-2.0450

The geometrical arrangements of the imidazolium (IMID) relative to the indole portion of the 5-HT congeners is shown in Figure 2 for the A-5 and A-6 configurations. We have shown that an optimal interaction between a relatively positive hydrogen and the indole nitrogen may be important for the enhancement of the polarization interaction [2], owing to the special properties of nitrogen as a "charge transducer" [5]. Consequently, one of the hydrogens in IMID is positioned above N1 in both the A-5 and the A-6 configurations. This position, and the alignment of the vector uniquely define the geometry of the complexes. Note, however, that due to geometrical constraints the hydrogen placed above N1 differs in the two configurations: in the A-5 configuration it is H1; in the A-6 configuration it is H4. It should be noted that H1 carries a more positive charge than H4 and is therefore expected to have a stronger effect on the polarization at the indole nitrogen.

In all the calculations, the geometries of the individual molecules were the same as described before [1,2] and unless otherwise specified, the intermolecular distance in all the complexes was kept constant at 6.238 a.u. (~3.3 Å) as described in Ref. 2. This distance is based on crystallographic data on the complexes of serotonin [6,7].



(a)

(b)

Figure 2. Orientation of 5-HT and 6-HT in complexes with IMID: (a) [5-HT + IMID] in A-5 configuration; (b) [6-HT + IMID] in A-6 configuration.

Methods of Calculation

Ab initio calculations were carried out for the isolated molecules and the complexes using the GAUSSIAN 70 program [8] with STO-3G and STO-4G basis sets [9]. Because our previous findings showed that the interaction with a negative receptor site can be simulated by a neutralization of the side chain, we calculated all tryptamine derivatives in their neutral forms (see Refs. 1 and 2 for details). The reactivity characteristics were analyzed as described in Ref. 1 from molecular electrostatic potential maps, electrostatic orientation vectors, and maps of electron-density distributions. In addition, we performed a decomposition of the interaction energies in the complex according to the scheme proposed by Morokuma [10]. In this scheme, the total stabilization energy of the complex is broken down into contributions from the electrostatic interaction of the unperturbed molecules (ES), a term related to the mutual polarization of the molecules (PL), the exchange repulsion (EX), and a composite term representing "charge-transfer" and additional energy contributions (CT + mix).

Results and Discussion

Stabilization Energies and the Nature of the Complexes

Table IV presents the stabilization energies of the 5-HT and 6-HT complexes with IMID in the geometries described in Figure 2 (see Methods section for the definition of the A-5 and A-6 configurations). The results show that for 5-HT the preferred geometry of the two possible configurations (A-5 and A-6) is that in which the imidazolium cation aligns its most positively charged regions with

TABLE IV. Energy decomposition in complexes with imidazolium.[a]

Type of contribution	5-HT + IMID at A-5	5-HT + IMID at A-6	6-HT + IMID at A-6	6-HT + IMID at A-5
ES	-4.52	-3.70	-4.51	-3.93
PL	-1.00	-0.98	-0.96	-1.00
EX	2.39	2.27	2.28	2.38
CT(+ mix)	-0.59	-0.38	-0.38	-0.59
Total stabilization	-3.72	-2.79	-3.57	-3.14

[a] Energy values are from calculations with the STO-3G basis set. Units are kcal/mol.

the electrostatic orientation vector of 5-HT (i.e., configuration A-5). For the [6-HT + IMID] complex the A-6 configuration is preferred over A-5. These results are in full agreement with the predictions made from reactivity criteria [1] regarding the differences in the preferred configurations that 5-HT and 6-HT would adopt toward the same polar site. These predictions were made on the basis of the difference in the overall pattern of the electrostatic potentials generated by 5-HT and 6-HT. Moreover, it appears that the electrostatic orientation vectors that were generated as force vectors from these potentials [1] could be useful indicators of the reactivity characteristics of the 5-HT congeners in interactions with molecules of the type of imidazolium cation. The underlying reason for the validity of these reactivity criteria was suggested by our findings [2] that the complexes [5-HT + IMID] and [5-HIND + IMID] are electrostatic in nature. The decomposition of the stabilization energies in the complexes with 5-HT and 6-HT supports this explanation: Table IV shows that for all the complexes, in all the configurations, the electrostatic interaction (ES) is the largest term. Moreover, it is evident from Table IV that the total energetic preferences for a given configuration (i.e., A-5 for the 5-HT complex, and A-6 for the 6-HT complex) is determined by the electrostatic contribution (ES): for a given configuration, either A-5 or A-6, the only energy term that is different in the 5-HT complex from the 6-HT complex is ES, while all the others (PL, EX, CT + mix) are virtually identical. Also, for the *same* complex (e.g., [5-HT + IMID]), only the ES values differ significantly between the A-5 and A-6 configurations. The very small contribution of the (CT + mix) term indicates that the main changes in the electron distributions of the molecules upon complex formation are in the form of charge polarization (see below).

The predictive value of the reactivity characteristics is thus suggested by these findings, and their possible validity is explained by the decomposition of the stabilization energy of the supermolecular model complexes.

Two important questions are related to the application of these reactivity criteria to the systems of interest:

(a) Since the orientation vectors are defined only on the indole portion of the tryptamine congeners, is there any direct interference of the side chain with the preferred configuration?

(b) Since the interplanar separations in the complex models were kept *fixed* at the crystallographic "close contact" distance of 3.3 Å (see Methods in Ref.

1), do the conclusions on the electrostatic nature of the interactions remain valid for the energetically most probable interaction distances between the tryptamine congeners and imidazolium?

Calculations on complexes between substituted indoles (e.g., 5-hydroxyindole (5-HIND), 6-hydroxyindole (6-HIND)) and imidazolium cation indicate the answer to these questions: Table V presents the stabilization energies and the energy decomposition terms for complexes of 5-HIND and 6-HIND with IMID. A comparison with Table IV shows that the energetic differences between the tryptamine and the indole complexes with imidazolium are insignificant both in the total stabilization energies and in most of the components. The only noticeable difference, albeit small, is in the polarization term (PL), which is greater in the tryptamine complexes than in the corresponding indole models. This difference is directly attributable to the inductive effect of the saturated, neutral side chain and is in full agreement with well-documented observations [11,12] as discussed before [2]. It appears, therefore, that in addition to its role in defining the directionality constraints of the interaction of the indole portions in these molecules, the side chain reinforces the electrostatic nature of the interaction.

Table VI shows that a preferred interplanar distance for the [5-HIND + IMID] complex in the A-5 geometry is 3.5 Å, i.e., slightly greater than the "close contact" distance from crystallographic data, but very close to the average in-

TABLE V. Energy decomposition in complexes with imidazolium.[a]

Type of contribution	5-HIND + IMID at A-5	5-HIND + IMID at A-6	6-HIND + IMID at A-6	6-HIND + IMID at A-5
ES	-4,62 (-4,76)	-3,89	-4,69	-4,03 (-4,14)
PL	-0,74 (-0,74)	-0,76	-0,74	-0,74 (-0,73)
EX	2,24 (2,54)	2,28	2,28	2,24 (2,54)
CT(+ mix)	-0,57 (-0,52)	-0,38	-0,38	-0,57 (-0,52)
Total stabilization	-3,69 (-3,48)	-2,75	-3,53	-3,10 (-2,85)

[a] Energy values are from calculations with the STO-3G basis set. Values in parentheses are from calculations with the STO-4G basis set. Units are kcal/mol.

TABLE VI. Energy decomposition in complexes 5-HIND + IMID at A-5.[a]

Type of contribution	Interplanar distance (Å)			
	3,796	3,51	3,301	2,971
ES	-3,60	-4,11	-4,62	-6,13
PL	-0,51	-0,63	-0,74	-0,99
EX	0,24	0,83	2,24	9,24
CT + mix	-0,08	-0,24	-0,57	-1,99
Total stabilization	-3,95	-4,15	-3,69	+0,13

[a] Energy values are from calculations with the STO-3G basis set. Units are kcal/mol.

TABLE VII. Planar densities[a] (in e/a.u.^{3}).

Distance from 5-HT plane (n)[b]	Molecule		
	5-HT	IMID	[5-HT + IMID][e]
-2	10.3753	0.0	10.3485
-1	18.6335	0.0	18.6035
0[c]	22.7109	0.0	22.7209
1	18.9313	0.0	18.9773
2	9.6830	0.0004	9.7166
3	3.7233	0.0033	3.7387
4	1.3457	0.0202	1.3665
5	0.3563	0.1165	0.4666
6	0.0770	0.4678	0.5371
7	0.0122	1.5182	1.5243
8	0.0014	4.2467	4.2427
9	0.0001	8.9324	8.9268
10[d]	0.0000	11.1506	11.1450
11	0.0	8.9324	8.9431
12	0.0	4.2467	4.2553

[a] Densities are calculated from molecular wave functions obtained with the pseudopotential method (see Ref. 2 for methodology details).

[b] Distances are expressed as n × 0.6238 a.u. (6.238 a.u. is the interplanar distance in the complex).

[c] Plane containing the indole portion of 5-HT.

[d] Plane containing the imidazolium molecule.

[e] The complex is in the A-5 configuration.

terring distance in the complexes of 5-HT [6,7]. It is evident from the energy decomposition presented in Table VI that the electrostatic nature of the complex is preserved at all relevant distances, as the ES component is the determinant factor in the total stabilization energy at distances greater than 3.1 Å. Identical conclusions hold for the [6-HIND + IMID] complex in the A-6 configuration.

Electron-Charge Distribution and Formation of Complexes

The electrostatic nature of the complexes and the relative contribution of polarization, exchange repulsion, and "charge transfer" terms to the stabilization energies indicated that the charge redistribution accompanying complex formation would be mainly "intramolecular" in character: the polarization within each molecule will enhance the electrostatic interaction but there will be little "overlap" or actual transfer of charge. With the STO-3G basis set, the Mulliken population analysis (which at an interplanar distance of 3.3 Å can be expected to reproduce well the charges within each component of the complex) indicates a minimal amount of charge transferred from 5-HT to IMID (0.0029 at A-5, and 0.0018 at A-6). The *same* results are obtained for the [6-HT + IMID] complex: 0.0029 and 0.0017 for the A-5 and A-6 configurations, respectively.

In order to study the detailed characteristics of the charge redistribution we used partial integrations of the total electron-density distribution function (ρ). The "planar density" (ρ^p), obtained by integrating ρ in a given plane, has been

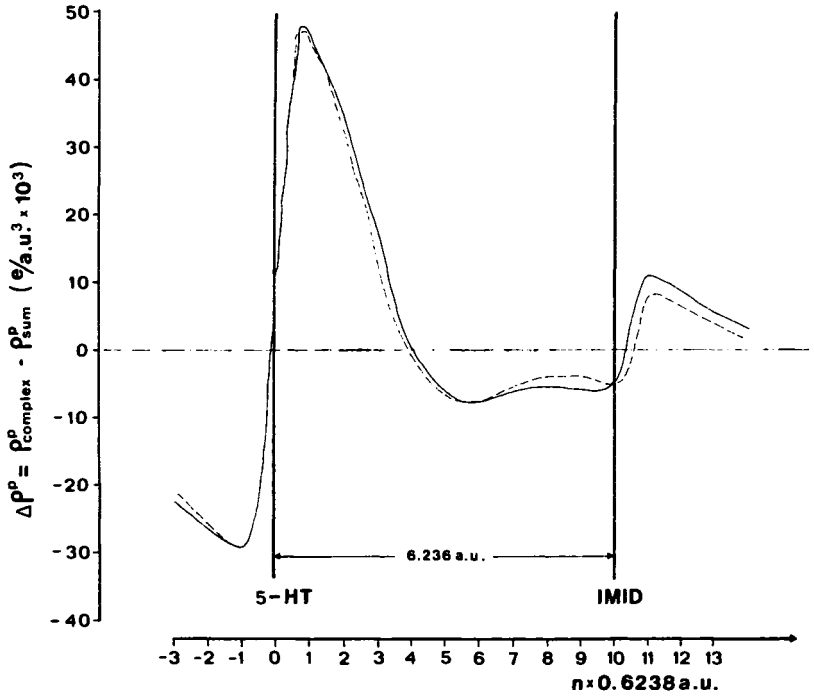


Figure 3. Electron-density redistribution in [5-HT + IMID] complexes in A-5 and A-6 configurations. $\rho^p(\mathbf{r})$ is the integrated density in a plane parallel to the indole portion of 5-HT, situated at a distance **r**. $\Delta\rho^p(\mathbf{r})$ is the difference between the plane-integrated density in the complex and the sum of the plane integrated distances of 5-HT and IMID, at a certain distance **r** from the indole portion. (—) A-5; (- - -) A-6.

calculated with Module PA60 of the POLYATOM program. (The POLYATOM program package was obtained from the Quantum Chemistry Program Exchange (QCPE No. 238), Indiana University.) Table VII shows the values of ρ^p in planes parallel to the indole portion of 5-HT. An expression of the charge redistribution upon complex formation is obtained from the difference between the ρ^p values for the complex (column 3 in Table VII) and the sum of the ρ^p values of the separated molecules (columns 1 and 2 in Table VII). This difference function ($\Delta\rho^p$) is plotted as a function of the intermolecular distance in Figure 3, and indicates that the charge in 5-HT has been strongly polarized *toward* IMID, while the charge in imidazolium cation is polarized *away* from 5-HT. This result is in full agreement with the basic idea that the polarizability of the 5-HT molecule is a major determinant of its ability to form molecular complexes, especially with a positively charged species. The polarization of the electronic charge in IMID will cause an increase in the positive electrostatic field generated by the molecule in the direction of 5-HT; this further increases the interaction with the excess electronic charge introduced in the interplanar region by the polarization of 5-HT.

Figure 3 also shows that the polarization pattern of the [5-HT + IMID] complex in the A-6 configuration will be very similar to that in the A-5 ar-

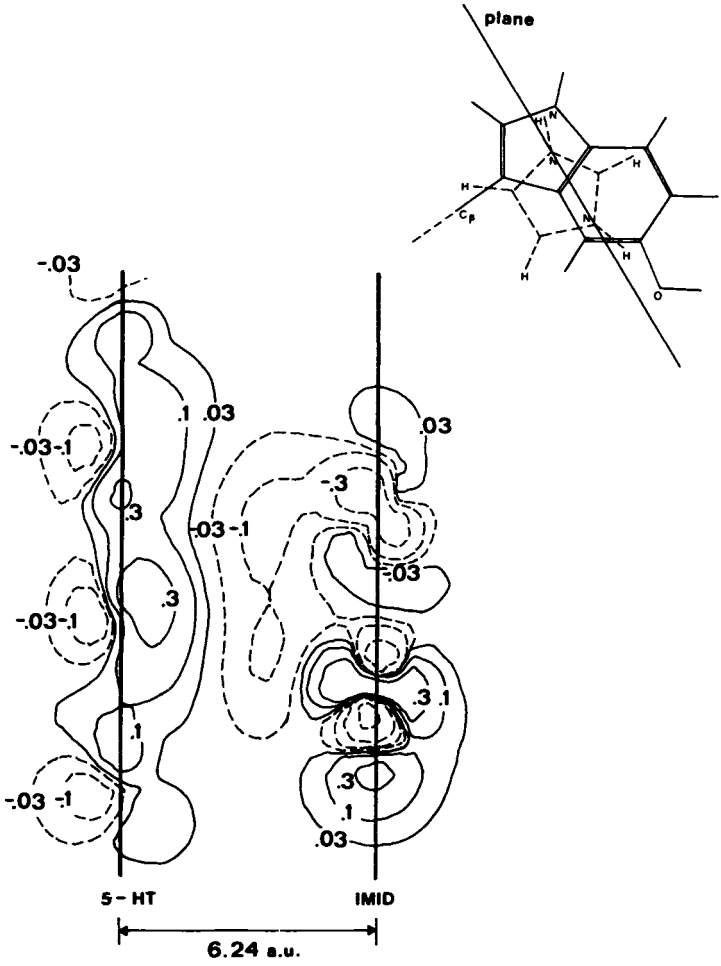


Figure 4. Density difference map in a plane perpendicular to the imidazole and indole ring portions of the [5-HT + IMID] complex, in the A-5 configuration. Insert shows the position of the plane relative to the complex. $\Delta\rho = \rho(\text{complex}) - \rho(\text{sum})$. (—) $\Delta\rho > 0$; (- - -) $\Delta\rho < 0$.

rangement (although very slightly less accentuated). This is in full agreement with the contribution of polarization (PL) to the stabilization of the complexes in the two configurations (see Tables IV and V). Since the contributions of the PL terms to the total stabilization of the [6-HT + IMID] and [6-HIND + IMID] complexes were nearly identical to those for the corresponding complexes of 5-HT and 5-HIND, it is not surprising that the same polarization pattern is observed in the complexes of 6-HT. This near identity holds not only for the integrated values of the charge distribution function, but also for the charge redistribution pattern in localized parts of the complex. This characteristic is exemplified in Figures 4 and 5 in which the changes in the total density upon complex formation ($\Delta\rho$) are calculated in equivalent planes for the [5-HT +

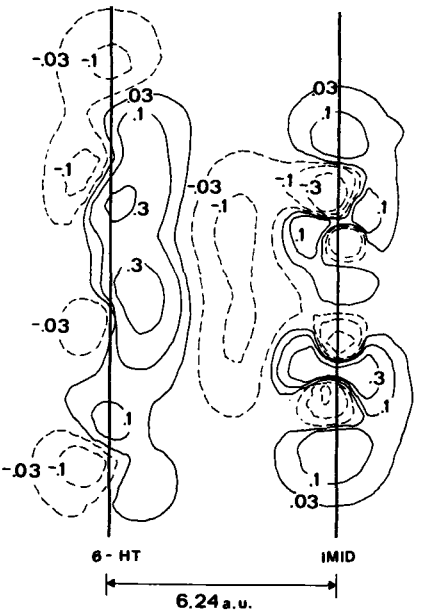


Figure 5. Density difference map in a plane perpendicular to the imidazole and indole ring portions of the [6-HT + IMID] complex, in the A-6 configuration. $\Delta\rho = \rho(\text{complex}) - \rho(\text{sum})$. (—) $\Delta\rho > 0$; (- - -) $\Delta\rho < 0$.

IMID] complex (Fig. 4), and the [6-HT + IMID] complex (Fig. 5). This finding is most important in view of the biological activity exhibited by 5-HT and 6-HT: *the mechanism of receptor activation is most likely to be the same for these compounds since they have the same effects and the same maximal activation ability ("intrinsic activity")*.

Our results therefore indicate that polarization complexes of the type analyzed here can provide a good model for the interaction mechanism of these molecules with the LSD–serotonin receptor. The results presented here are consistent with the idea that the orientation vectors can predict the preferred geometry of interaction in these models. The predictor value of the vectors can be confirmed by a full scan of the energy as a function of the configuration in complexes of different congeners with IMID. We are carrying out further calculations to confirm this predictor function of the vectors.

The results presented here also indicate that once a congener (e.g., 6-HT) is forced to adopt an interaction geometry that aligns its vector with that of the common reactant (albeit with lower probability), the *consequences* of the interaction are identical. Other members of the congeneric series of singly substituted tryptamine derivatives are expected to exhibit the same type of reactivity characteristics:

(i) Formation of polarization complexes with a variable degree of probability (dependent on their molecular structure and predictable by the reactivity parameters).

(ii) Generation of charge redistribution patterns that are very similar to those

of 5-HT once an equivalent interaction geometry is adopted with the receptor site.

At the present level of biological experimentation the implications of our working hypothesis for the pharmacological activity of tryptamine congeners on the LSD–serotonin receptor can be tested by the prediction of structures with similar electrostatic orientation preference to 5-HT that can also generate the same charge redistribution in a model reactant (such as IMID). Since the reactivity parameters discussed above are defined independent of the molecular structure, the proposed drugs need not share the structure of the tryptamine derivatives. Such goals have been achieved before in other series of drugs [13,14] and this seems to be a most promising avenue for further investigation.

Acknowledgments

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