A QUANTUM-CHEMICAL CORRELATE OF HALLUCINOGENESIS

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HALLUCINOGENIC drugs have been studied extensively in recent years, both as tools for the production of experimental psychosis and as possible therapeutic agents in mental disease. The striking effects of these drugs on the human mind have intrigued layman and scientists alike. Although the therapeutic usefulness and the authenticity of the "schizophreniform" state following drug ingestion has been debated, it is likely that an understanding of the mechanisms of action of hallucinogenic drugs will be of considerable heuristic value in the study of the biochemical basis of mental function.

While many drugs affect mental activity, and various drug-induced psychoses have been described, the term "hallucinogen" as used here will refer only to a restricted group of compounds, whose effects are quite similar and, in some studies, indistinguishable (Ungar, 1963). There are two major chemical classes of hallucinogens: those resembling tryptamine, such as psilocin and *d*-lysergic acid diethylamide (LSD); and those related to phenylethylamine, such as mescaline and 3,4,5-trimethoxyamphetamine, (TMA). The clinical resemblance of the syndromes produced by mescaline, psilocin, LSD, TMA and other hallucinogens suggests that these drugs, despite differences in chemical structure, may share a common mechanism of action. The fact that the psychotropic effects of TMA, a methoxylated amphetamine, are quite unlike those of amphetamine but strikingly similar to those of LSD, a complex alkaloid, illustrates the complexity of structure-activity relationships of hallucinogens. The hypothesis that hallucinogens possess a common mechanism of action is supported by findings that cross-tolerance can develop between the hallucinogens, LSD, mescaline, and psilocybin (Balestrieri and Fontanari, 1959; Isbell *et al.*, 1961), but not between hallucinogens and amphetamine (Isbell *et al.*, 1962), or scopolamine (Isbell *et al.*, 1964).

There are other structure-activity relationships of hallucinogens which are not easily explained. The introduction of bromine at carbon 2 of LSD

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(Cerletti and Rothlin, 1955), or the reduction of a double bond between carbons 9 and 10 of LSD (Cerletti, 1959), renders the molecule devoid of hallucinatory activity. Minor structural changes in the TMA series produce marked changes in hallucinogenic activity. Shulgin (1964) has found that TMA-2 (2,4,5-trimethoxyamphetamine) is about seventeen times as potent an hallucinogen as mescaline; that TMA (3,4,5-trimethoxyamphetamine) is about twice as active as mescaline; and that TMA-3 (4,5,6-trimethoxyamphetamine) is devoid of hallucinogenic activity. Of the N-methylated tryptamines, psilocin (4-hydroxy-N,N-dimethyltryptamine) is a potent hallucinogen (Wolbach *et al.*, 1962), while bufotenine (5-hydroxy-N,N-dimethyltryptamine) is inactive (Turner and Merles, 1959; H. Isbell, personal communication).

Hypotheses for the mechanism of hallucinogenic activity of drugs ideally should explain all the structure-activity relationships described above. Since the presumed brain neurohumors, norepinephrine and serotonin, are structurally similar to phenylethylamine and tryptamine, respectively (the prototypes for the two major classes of hallucinogens), it has been thought that hallucinogens might affect synaptic transmission in the brain. One theory postulates that hallucinogens act in the brain as anti-metabolites of serotonin (Wooley and Shaw, 1954), and is based on the finding that LSD in low concentrations antagonizes the contractile effect of serotonin on smooth muscle. However, 2-brom-LSD, which has 50% more anti-serotonin activity than LSD on the estrous rat uterus, and which readily enters the brain, has no hallucinogenic activity (Cerletti and Rothlin, 1955).

The apparent lack of a simple relationship between molecular architecture and the hallucinogenic potency of drugs is perplexing. In our laboratories, molecular models of active hallucinogens and their less active analogs were constructed and compared. This comparison failed to reveal any remarkable properties of the active compounds. It was therefore considered that the critical feature of hallucinogens might reside not in their gross chemical structure but in the distribution of electrons.

An electronic, or "sub-molecular" hypothesis for the psychotic actions of drugs is not altogether novel. Karreman *et al.* (1959) had performed molecular orbital calculations for a series of psychoactive drugs. They noted that chlorpromazine is an extraordinarily potent electron donor and suggested that its efficacy as a tranquilizer may be related to an electron-donating action. Isenberg and Szent-Gyorgyi (1959) found experimentally that serotonin readily donates electrons to form charge transfer complexes. Szent-Gyorgyi (1960) speculated that schizophrenia might involve a paucity of cerebral electronic activity, reversed by chlorpromazine treatment.

Molecular orbital calculations such as those performed by Karreman *et al.* (1959) afford an approximation of the electronic configuration of pi systems of molecules. From such calculations, measures of chemical reactivity can be ascertained for a given molecule and compared with any given property in

order to define a correlation between function and electronic configuration.

Molecular orbital calculations have been made for a variety of hallucinogenic drugs and their non-hallucinogenic analogs in order to seek such correlations. A striking relationship has been observed between electronic configuration and hallucinogenic potency in several series of phenylethylamine, amphetamine, and tryptamine derivatives, and for LSD.

METHODS

Molecular orbital calculations were made by the semi-empirical Hückel method (Streitweiser, 1961), using a Honeywell 800 digital computer with a program designed by Howard de Voe. The authors wish to express their appreciation to Dr. Howard de Voe for the use of his program and for assisting us in its modification. The simple Hückel molecular orbital calculations deal only with pi-bonded systems and cannot take into account sigma bonds. Since all of the compounds in this study contain sigma-bonded side chains, an approximation was made for the side chains. Comparison of reactivity indices were made between compounds with similar side chains. Parameter values were those suggested by Streitweiser (1961). The following reactivity indices were determined: pi charge, free valence, frontier electron density, superdelocalizability, and the energies of the highest filled and lowest empty molecular orbitals.

Pi charge represents the net positive or negative electrical charge measured at each atom of a molecule. This index provides a relative indication of the capacity to participate in electrostatic interactions.

Free valence (Streitweiser, 1961) measures the residual pi bonding which is available to form a weak pi bond linkage with an attacking reagent.

The energy of the highest filled molecular orbital (HFMO) is a relative measure of the ability of an electron in the highest occupied molecular orbital of a compound to be transferred to an acceptor molecule. The higher the HFMO energy, the greater will be the propensity of a molecule to donate electrons. The energy of the lowest empty orbital (LEMO) indicates the ease with which an electron can be accepted from a potential donor.

Frontier electron density is the spatial distribution of the electrons in the HFMO. Thus an atom with a high frontier electron density would have a greater density of HFMO electrons than an atom with a low frontier electron density (Fukui *et al.*, 1957).

Superdelocalizability (Fukui *et al.*, 1952) is a measure of the ability of each atom in a molecule to form a weak pi bond with an incoming attacking reagent when the pi system remains unperturbed. In the present study superdelocalizability was calculated for all atoms in each molecule, but is reported only for the atom with the highest frontier electron density.

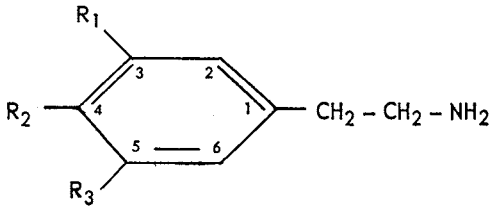
TABLE 1. ELECTRONIC CONFIGURATION OF PHENYLETHYLAMINES

Compound	HFMO†	Highest free valence	Greatest negative pi charge		Greatest frontier electron density		Super-delocalizability‡	LEMO†
			Position		Position		Position	
Mescaline (3,4,5-trimethoxyphenylethylamine)	+0·5357	1·72	CH_3 at 4	−0·104	2, 6	0·5122	4	1·23	−1·12
2,3,4-Trimethoxyphenylethylamine	+0·5696	1·72	CH_3 at 4, 5, 6	−0·072	3	0·3960	4	1·05	−1·10
3,4-Dimethoxydopamine	+0·5702	1·72	CH_3 at 4	−0·074	2	0·4162	4	1·06	−1·05
4-Methoxydopamine	+0·6016	1·72	CH_3 at 4	−0·071	2	0·4341	4	1·02	−1·04
3-Methoxydopamine	+0·6184	1·72	CH_3 at 3	−0·074	2	0·4690	4	1·05	−1·05
Methoxytryramine	+0·6583	1·71	CH_3 at 3	−0·041	2	0·3894	4	0·95	−1·03
Methoxymetatyramine	+0·7240	1·71	CH_3 at 3	−0·076	2	0·3595	4	1·05	−1·03
3,4,5-Trihydroxyphenylethylamine	+0·6316	1·51	O_2 at 4	−0·097	2, 6	0·6111	4	1·16	−1·11
Dopamine	+0·6586	1·50	O_2 at 4	−0·071	2	0·5191	4	1·02	−1·04
Tyramine	+0·7209	1·49	O_2 at 4	−0·038	3, 5	0·5017	1	0·92	−1·00
Metatyramine	+0·7240	1·48	O_2 at 3	−0·072	2	0·4834	6	1·02	−1·03
Phenylethylamine	+0·8619	0·41	6, 2	−0·031	4	0·5771	4	0·91	−1·00

† Expressed in β units so that mescaline is a better electron donor and a poorer acceptor than phenylethylamine.
‡ Expressed in reciprocal β units; thus mescaline is a better electron donor than phenylethylamine.

RESULTS AND DISCUSSION

Molecular orbital calculations were performed for series of mono-, di-, and trihydroxylated and methoxylated phenylethylamines (Fig. 1; Table 1). Progressive methoxylation was found to correlate with an increase in HFMO energy. With monophenolic amines, such as tyramine and metatyramine, and the diphenolic amine dopamine, the methoxy derivatives had more energetic HFMO's than the corresponding hydroxylated derivatives. A more energetic HFMO is indicated by a lower value in β units. Moreover, additional hydroxy groups also increased the HFMO energy. Thus 3,4-dihydroxyphenylethylamine had a more energetic HFMO than the monophenolic



COMPOUND	R_1	R_2	R_3
Dopamine	OH	OH	–
3-Methoxydopamine	CH_3O	OH	–
3-4-dimethoxyphenylethylamine	CH_3O	CH_3O	–
Mescaline	CH_3O	CH_3O	CH_3O
Tyramine	–	OH	–
Phenylethylamine	–	–	–

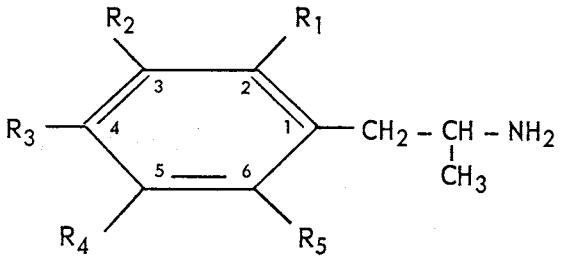
FIG. 1. The structures of several phenylethylamine derivatives.

derivatives, and 3,4,5-trihydroxyphenylethylamine had the highest HFMO energy of the phenolic amines. Highest HFMO energy levels occurred in compounds with the most methoxy substituents. Mescaline, a molecule in which all three hydroxy groups are methylated, had the most energetic HFMO of the series. The second highest value was considerably less energetic and occurred in 2,3,4-trimethoxyphenylethylamine. Progressive methoxylation also correlated with superdelocalizability, which is a function of the HFMO energy related to each atom.

There was a negative correlation between the number of methoxy groups and the energy of the lowest empty molecular orbital (LEMO). This would indicate that progressive methoxylation decreases the capacity of these compounds to function as electron acceptors. No clear-cut correlation was

obtained between the number of methoxy substituents and frontier electron density, free valence or pi charge.

Mescaline (3,4,5-trimethoxyphenylethylamine) is well known as an effective hallucinogen. Transposition of one methoxy group from the No. 5 position to the No. 2 position (to form 2,3,4-trimethoxyphenylethylamine) results in a molecule which is devoid of hallucinogenic activity (Slotta and Muller, 1936). Data on the effects of 3,4-dimethyoxyphenylethylamine in humans are lacking. Direct information regarding central effects of phenolic amines, such as dopamine and tyramine, is difficult to obtain, since these compounds do not cross the blood brain barrier. However, the concentration of both dopamine



COMPOUND	R_1	R_2	R_3	R_4	R_5
TMA	–	CH_3O	CH_3O	CH_3O	–
TMA-2	CH_3O	–	CH_3O	CH_3O	–
TMA-3	–	–	CH_3O	CH_3O	CH_3O

FIG. 2. The structures of three trimethoxylated amphetamine derivatives.

and tyramine in the brain can be markedly elevated in animals following treatment with monoamine oxidase inhibitors (Kakimoto and Armstrong, 1962; Carlsson *et al.*, 1960). Brain dopamine concentration can also be increased by the administration of its amino-acid precursor, dihydroxyphenylalanine (Weil-Malherbe and Bone, 1959). Neither monoamine oxidase inhibition nor dihydroxyphenylalanine treatment produces effects comparable to those of mescaline. Yet, the characteristic effects of mescaline on mental functioning presumably occur when brain levels of the drug are less than 1 μg/g (Neff *et al.*, 1964), and thus lower than brain levels of dopamine obtained after monoamine oxidase inhibition or dihydroxyphenylalanine treatment.

There would therefore appear to be a possible relationship between the hallucinogenic activity of phenylethylamines and the ability of these compounds to donate electrons, as indicated by the energy of the HFMO's.

TABLE 2. AMPHETAMINE DERIVATIVES: ELECTRONIC CONFIGURATION AND HALLUCINOGENIC POTENCY

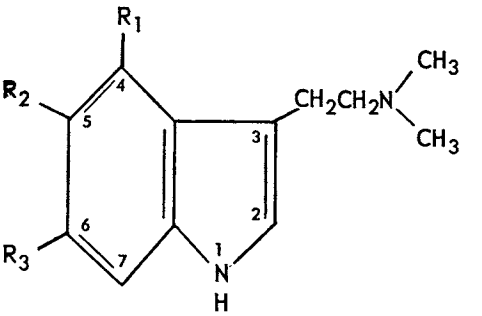
Compound	Hallucinogenic activity§	HFMO†	Highest free valence	Greatest negative pi charge		Greatest frontier electron density		Super-delocalizability‡		LEMO†
				Position		Position		Position		
TMA-2	17	0·4810	1·72	CH_3 at 2, 4, 5	−0·0854	3	0·3675	5	1·14	−1·072
TMA	2·2	0·5357	1·72	CH_3 at 4	−0·1040	2, 6	0·5122	4	1·23	−1·116
TMA-3	2	0·5696	1·72	CH_3 at 4, 5, 6	−0·0716	3	0·3960	4	1·05	−1·105

† Expressed in β units so that TMA-2 is a better electron donor and poorer acceptor than TMA-3.

‡ Expressed in reciprocal β units so that TMA is a better electron donor than TMA-3.

§ Hallucinogenic activity values are those of Shulgin (1964) and are expressed as the ratio of the effective dose of mescaline in humans (3·75 mg/kg) to the effective dose of a given drug.

To test this correlation in another series, calculations were performed for a group of trimethoxyamphetamines (Fig. 2; Table 2) of widely varying hallucinogenic activity. TMA-2 (2,4,5-trimethoxyamphetamine) and TMA (3,4,5-trimethoxyamphetamine) are respectively about seventeen times and two times more potent then mescaline as hallucinogens, whereas TMA-3 (4,5,6-trimethoxyamphetamine) appears to be inactive (Shulgin, 1964). The three drugs differ structurally only in the location of their methoxy substituents. The presence of both ring and side chain methyl groups should enable all three to enter the brain readily and to a similar extent. Calculations revealed marked differences in the HFMO energies of these three compounds which correlated with the differences in their hallucinogenic potency. Thus, TMA-2



COMPOUND	R_1	R_2	R_3
Dimethyltryptamine	H	H	H
Bufotenine	H	OH	H
6-Hydroxy-N-N-dimethyltryptamine	H	H	OH
Psilocin (4-Hydroxy-N-N-dimethyltryptamine)	OH	H	H

FIG. 3. The structures of several N-alkylated tryptamine derivatives.

had the most energetic HFMO, TMA-3 the least, and TMA was intermediate. Hallucinogenic potency did not correlate with frontier electron density, pi charge, free valence, superdelocalizability, or energy of the LEMO.

Since the Hückel determinations employed here do not take into account sigma bond alterations in the side chains, the calculated electronic configurations for TMA and TMA-3, respectively, are the same as for mescaline and 2,3,4-trimethoxyphenylamine. It is, therefore, interesting that hallucinogenic potency parallels HFMO energy in the same way for these four molecules.

Several N-alkylated tryptamine derivatives produce hallucinogenic effects in human subjects which are qualitatively similar to those associated with mescaline and LSD (Szara, 1957). Calculations were performed on a series of these compounds (Fig. 3; Table 3). The energy of the HFMO was greatest

TABLE 3. TRYPTAMINE DERIVATIVES: ELECTRONIC CONFIGURATION AND HALLUCINOGENIC POTENCY

Compound	Hallucinogenic activity‖	HFMO‡	Highest free valence		Largest negative pi charge		Greatest frontier electron density		Super-delocalizability§	LEMO†
				Position		Position		Position		
Psilocin	31	0·4603	1·48	O_2 at 4	−0·077	9	0·5118	2	−1·53	−0·882
6-Hydroxydiethyl-tryptamine	25	0·4700	1·49	O_2 at 6	−0·080	3	0·5664	2	−1·53	−0·871
Bufotenine	—†	0·5147	1·49	O_2 at 5	−0·084	3	0·5435	2	−1·43	−0·839
Diethyltryptamine	—†	0·5164	0·99	1	−0·081	3	0·5739	2	−1·43	−0·838

† Weak or inactive as detailed in text.
‡ Expressed in β units so that psilocin is a better electron donor and poorer acceptor than dimethyltryptamine.
§ Expressed in reciprocal β units; thus psilocin is a better electron donor than dimethyltryptamine.
‖ Expressed as ratio of effective dose of mescaline to effective dose of a given drug. Values for psilocin were obtained from Wolbach *et al.* (1962) and for 6-hydroxydiethyltryptamine from Szara (1957).

for psilocin (4-hydroxy-N,N-dimethyltryptamine) and next highest for 6-hydroxy-N,N-diethyl or dimethyltryptamine.[1] Corresponding values for bufotenine (5-hydroxy-N,N-dimethyltryptamine) and N,N-dimethyltryptamine (or N,N-diethyltryptamine) were considerably lower. Psilocin is the most potent hallucinogen of these drugs (Wolbach *et al.*, 1962) and 6-hydroxy-N,N-diethyltryptamine is next most effective (Szara, 1962). The administration of N,N-dimethyltryptamine or N,N-diethyltryptamine does produce hallucinogenic effects (Szara, 1957) but the available evidence indicates that these compounds and bufotenine of themselves are weak or ineffective as compared to psilocin and 6-hydroxy-N,N-diethyltryptamine.

Fabing and Hawkins (1956) observed minor alterations in visual perception and paresthesias in normal subjects after the intravenous injection of bufotenine. There were, however, no control subjects in this study to rule out possible placebo effects. Other workers (Turner and Merles, 1959; H. Isbell, personal communication) administered a variety of drugs as well as saline controls to schizophrenics and to normal subjects. Bufotenine in doses up to twice those used by Fabing and Hawkins (1956) was without hallucinogenic effect.

The parenteral administration of dimethyl or diethyltryptamine to human subjects results in hallucinogenic experiences similar to those produced by LSD or mescaline, but of more rapid onset and shorter duration (Szara, 1957). Szara has found that these drugs are 6-hydroxylated in the liver (Szara and Axelrod, 1959) and that their psychotropic activity is closely related to the extent of 6-hydroxylation (Szara and Hearst, 1962). Moreover, 6-fluorodiethyltryptamine, a molecule which cannot be 6-hydroxylated *in vivo*, is devoid of hallucinogenic activity (Kalier and Szara, 1963). These data, as well as the observation that 6-hydroxy-N,N-diethyltryptamine in doses of 0·14 mg/kg can produce psychotropic effects comparable to those evoked by 1·0 mg/kg of N,N-diethyltryptamine (Szara and Hearst, 1962), have led Szara to conclude that the characteristic symptoms associated with diethyl- or dimethyltryptamine administration are mediated by their 6-hydroxylated metabolites.

There appears, therefore, to be an excellent correlation between hallucinogenicity of the tryptamine derivatives and the energy of their HFMO. Superdelocalizability, a function of the HFMO energy, also correlated with hallucinogenic potency. There was a negative correlation with the energy of the LEMO and no correlation with pi charge, frontier electron density, or free valence.

To provide an indication of the distribution of various electronic parameters throughout each molecule, the free valence, frontier electron density, superdelocalizability, and pi charge for mescaline appear in Fig. 5. Comparable values for TMA-2 and psilocin appear in Figs. 4 and 6 respectively.

[1] The molecular orbital calculations used in this study do not distinguish between N,N-dimethyl- or N,N-diethyltryptamines.

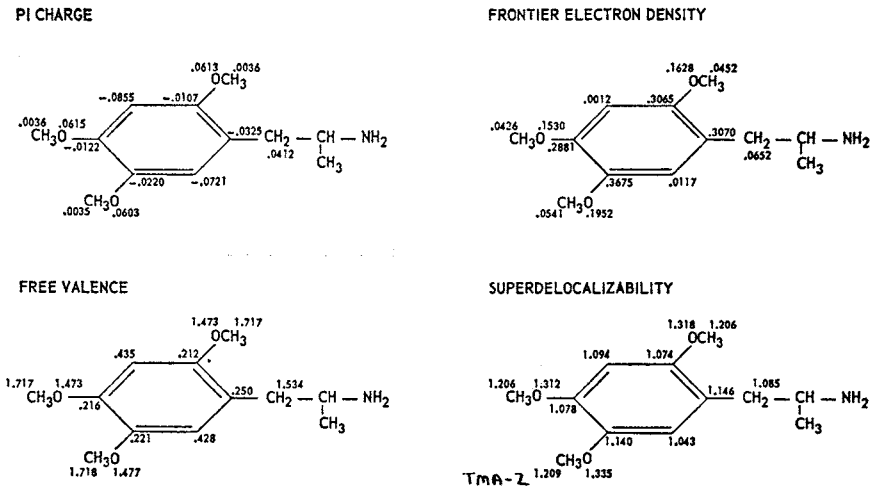


FIG. 4. Electronic reactivity indices for ~~mescaline~~. Superdelocalizability is expressed in reciprocal β units.

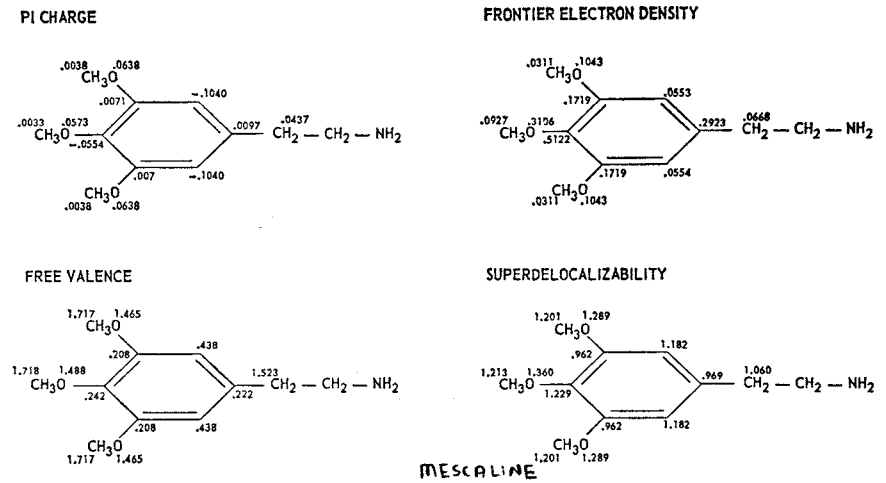
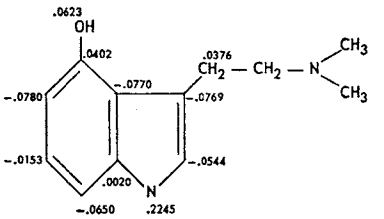
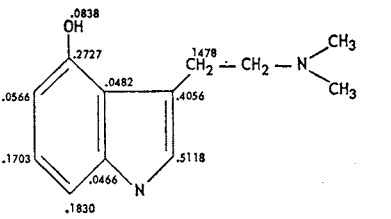


FIG. 5. Electronic reactivity indices for ~~TMA-2~~. Superdelocalizability is given in reciprocal β units.

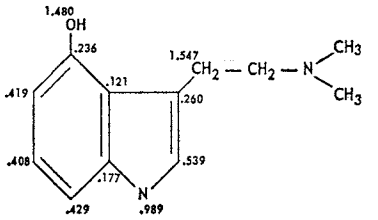
PI CHARGE



FRONTIER ELECTRON DENSITY



FREE VALENCE



SUPERDELOCALIZABILITY

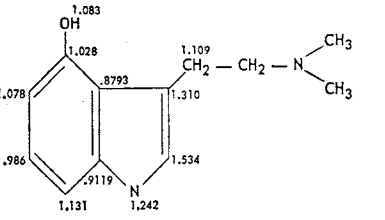


FIG. 6. Electronic reactivity indices for psilocin. Superdelocalizability is expressed in reciprocal β units.

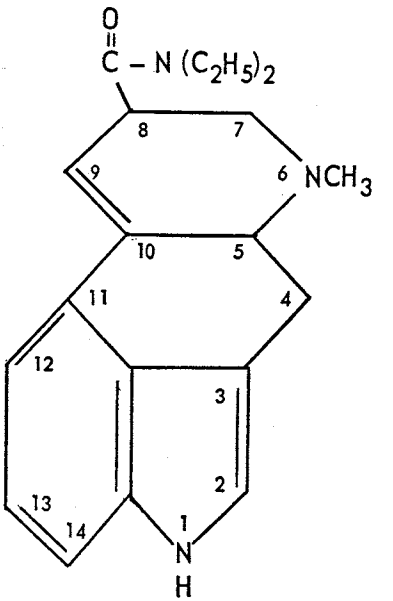


FIG. 7. The structure of *d*-lysergic acid diethylamide.

The best known and most potent hallucinogen is LSD, which is highly effective in humans at doses of 1 μg/kg. The LSD molecule (Fig. 7) contains an indole nucleus linked to two other sigma-bonded ring systems. Since the computer program used in this study to determine electronic indices cannot take into account sigma-bonded systems, a detailed electronic configuration could not be determined for LSD. If, however, the effect of the saturated ring system on the indole nucleus is approximated by the introduction of methyl groups at positions Nos. 3 and 4, a crude calculation can be performed. Such a methylated indole model of LSD has a calculated energy of the HFMO of 0·474 β units as compared to a value of 0·516 for N,N-dimethyltryptamine which contains an unsubstituted indole ring. Karreman *et al.* (1959) calculated the HFMO energy for the complete LSD molecule and obtained a value of

TABLE 4. RELATIONSHIP OF HALLUCINOGENIC POTENCY IN DIFFERENT CLASSES OF DRUGS TO THE ENERGY OF THEIR HFMO

Drug	Minimum effective dose (mg/kg)	Hallucinogenic activity†	Energy of HFMO§
LSD	0·001	3700	0·2180‡
Psilocin	0·12	31	0·4603
6-Hydroxydiethyltryptamine	0·15	25	0·4700
TMA-2	0·22	17	0·4810
TMA	1·70	2·2	0·5357

† Hallucinogenic activity is expressed as ratio of effective dose of mescaline (3·75 mg/kg as the base) to the effective dose of a given drug.
‡ As determined by Karreman *et al.* (1959).
§ Expressed in β units; thus LSD is a better electron donor than TMA.

0·218 β units, indicating an HFMO far more energetic than any of the compounds examined in this study. As with all the tryptamine derivatives examined, the region of highest frontier electron density in LSD is at the No. 2 carbon atom. The position of greatest frontier electron density in a molecule is the probable active site for charge transfer reactivity. If a charge transfer mechanism is involved in the hallucinogenic action of LSD, the No. 2 carbon should be critical for this activity. It is, therefore, interesting to note that 2-brom-LSD (Cerletti and Rothlin, 1955) and 2-oxy-LSD (Axelrod *et al.*, 1957), which contain sterically obstructing substituents at the No. 2 carbon, are devoid of hallucinogenic effect, even though they readily enter the brain.

The energy of a pi system of electrons is closely related to the extent of the resonance within the system. A major factor in increasing the HFMO energy of LSD over that of a simple indole structure such as tryptamine lies in the possibility of resonance between the indole ring and the pi electrons of the double bond at C_9—C_{10} (Fig. 4). Although we cannot perform the appropriate calculations, it is likely that reduction of the double bond at C_9—C_{10}

would markedly decrease the HFMO energy for the LSD molecule. It is important, therefore, to note that the loss of the C_9—C_{10} double bond by hydrogenation or hydration (as in dihydro-LSD and Lumi-LSD respectively) abolishes the hallucinogenic properties (Cerletti, 1959).

The correlations between electronic configuration and hallucinogenic properties discussed above have been obtained within series of structurally related compounds. It would be important if such correlations could be obtained between groups of structually dissimilar drugs. It is unlikely that such a relationship could be established in detail. The action of a drug on its receptor in the brain is certainly several steps removed from its administration. Intervening are such critical variables as relative metabolic degradation, penetration of the blood brain barrier, and concentration into presumed target areas within the brain. The amphetamine and tryptamine analogs for which hallucinogenic efficacy, minimum effective dose, and electronic configuration are reasonably well established, have been grouped in Table 4, revealing a close correlation between hallucinogenic potency and HFMO energy.

The observed relationships between reactivity indices and psychotropic activity suggests the possibility of predicting the structure of hallucinogens even more potent than those presently available. Calculations for several hypothetical tryptamine derivatives (Table 5) indicate that methoxylation and disubstitution increase the energy of the HFMO. Thus dimethoxylated derivatives, such as 4,6-dimethoxy-N,N-dimethyltryptamine have the most energetic HFMO's.

The correlative data described here suggest a common mode of action for these hallucinogens at a hypothetical receptor. To support this view are studies which indicate that cross-tolerance can develop between LSD, psilocybin, and mescaline, (Balestrieri and Fontanari, 1959; Isbell *et al.*, 1961).

It would be interesting to postulate an electronic model for the interaction of an hallucinogenic drug with its receptor. The calculations performed in this study, however, do not permit a specific formulation. The energy of the highest filled molecular orbital of a compound is not a precise index; the correlation of HFMO energy with hallucinogenic activity only implies that these compounds may act as electron donors, but does not describe a mechanism for hallucinogenesis. Reactions involving electron donation cover a broad spectrum including such strong interactions of donor and acceptor as oxidation-reduction, as well as such weak interactions as charge transfer or acid-base phenomena. Moreover, the crudeness of the theoretical and pharmacological data in this study preclude a detailed delineation of the nature of the electron-donation process, as might be afforded by indices, such as free valence and superdelocalizability.

Correlation with an index of electron donation, and not with other indices of chemical reactivity is none the less useful. There are a great number of

TABLE 5. TRYPTAMINE DERIVATIVES WITH INCREASED HFMO ENERGY

Compound	HFMO†	LEMO†	Greatest frontier electron density		Super-delocalizability‡	Greatest negative pi charge		Greatest free valence	
				Position			Position		Position
4-Methoxypsilocin	0·4402	−0·8854	0·4753	2	1·558	−0·0822	5	1·714	CH_3 at 4
4,6-Dihydroxydimethyltryptamine	0·4231	−0·9227	0·5248	2	1·649	−0·1110	5	1·487	O_2 at 6
6-Methoxy-4-hydroxy-dimethyltryptamine	0·4099	−0·9257	0·5142	2	1·675	−0·1151	7	1·716	CH_3 at 6
4-Methoxy-6-hydroxy-dimethyltryptamine	0·4070	−0·9264	0·4972	2	1·675	−0·1156	5	1·714	CH_3 at 4
4,6-Dimethoxydimethyltryptamine	0·3954	−0·9294	0·4917	2	1·701	−0·1187	7	1·716	CH_3 at 6

† Expressed in β units so that 4,6-dimethoxydimethyltryptamine is a better electron donor and poorer acceptor than 4-methoxypsilocin.
‡ Expressed in reciprocal β units; thus, 4,6-dimethoxydimethyltryptamine is a better electron donor than 4-methoxypsilocin.

conceivable interactions between drug and receptor. The drug could sterically approximate the receptor, be bound by electrostatic interactions, form a weak covalent linkage, or act as an electron donor or acceptor. While steric factors are certainly important, they do not explain some structure-activity relationships, such as the greater efficacy of 2,4,5-trimethoxyamphetamine as compared to 4,5,6- or 3,4,5-trimethoxyamphetamines. The absence of correlation with pi charge distribution would tend to be inconsistent with an electrostatic attraction. And, if an electron transfer mechanism is involved, the negative correlation with energy of the lowest empty orbital would indicate that the hallucinogens do not exert pharmacological activity via electron acceptance.

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