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A RELATIONSHIP BETWEEN THE HALLUCINOGENIC ACTIVITY OF DRUGS AND THEIR ELECTRONIC CONFIGURATION

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The hallucinogens are compounds of differing structures which are capable of producing profound and qualitatively similar effects on the subjective mental functioning of human subjects. Structurally, there are two major classes: those resembling tryptamine, such as d-lysergic acid diethylamide (LSD), and those related to phenylethylamine, such as mescaline. Since the presumed brain neurohumors, norepinephrine and serotonin, are structurally similar to phenylethylamine and tryptamine, respectively, it has been thought that hallucinogens might affect synaptic transmission in the brain. One theory postulates that hallucinogens may act in the brain as antimetabolites of serotonin,[1] and is based on the finding that LSD in low concentrations antagonizes the contractile effect of serotonin on smooth muscle.[2] However, 2-brom-LSD, which has 50 per cent more antiserotonin activity than LSD on smooth muscle and which readily enters the brain, has no hallucinogenic activity.[3] Mescaline, an effective hallucinogen, is devoid of antiserotonin activity on the rat uterus.[4]

An electronic, or "submolecular," hypothesis for the psychotropic actions of drug has been proposed by Karreman, Isenberg, and Szent-Györgyi.[5] They performed molecular orbital calculations for chlorpromazine, LSD, and serotonin and concluded that these drugs were potent electron donors. They suggested that the

efficacy of chlorpromazine as a tranquilizer may be related to an electron donating action.

In the present study, molecular orbital calculations have been made for several series of hallucinogenic drugs and their nonhallucinogenic structural analogues. The relationship between electronic configuration and hallucinogenic potency has been examined for a variety of phenylethylamine, amphetamine, and tryptamine derivatives, and for LSD.

Methods.—Molecular orbital calculations were made by the semiempirical Hückel method,[6] using a Honeywell 800 digital computer with a program designed by Howard de Voe. (We wish to express our appreciation to Dr. 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, by treating them as a methyl heteroatom bonded to the pi system.[7] Comparison of reactivity indices were made between compounds with similar side chains. Parameter values for all heteroatoms were those suggested by Streitweiser.[7]

Electronic configurations were compared among structurally similar compounds. This was done to reduce possible errors due to choosing a poor parameter value. Thus, any particular parameter value would have a similar effect on calculations performed for all compounds in the series. The absolute values of the indices calculated might vary, but the relative differences between the compounds would not be affected.

The following reactivity indices were determined: pi charge, free valence, frontier electron density, superdelocalizability, and the energies of the highest occupied 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[8] measures the residual pi bonding which is available to form a weak pi bond linkage with an attacking reagent. The energy of the highest occupied molecular orbital (HOMO) 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 greater the HOMO energy, the greater will be the propensity of a molecule to donate electrons. In this study, molecular orbital energies are represented in β-units. Since β is a negative energy term, more energetic HOMO's are indicated by smaller values in β units. The energy of the lowest empty orbital 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 HOMO. Thus an atom with a high frontier electron density would have a greater density of HOMO electrons than an atom with a low frontier electron density.[9, 10] Superdelocalizability[11] 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.

Results and Discussion.—Molecular orbital calculations were made for series of mono-, di-, and trihydroxylated and methoxylated phenylethylamines (Fig. 1; Table 1). Progressive methoxylation was found to correlate with an increase in HOMO energy. With monophenolic amines, such as tyramine and metatyramine, and the diphenolic amine dopamine, the methoxy derivatives had more energetic HOMO's than the corresponding hydroxylated derivatives. Moreover, additional hydroxy groups also increased the HOMO energy. Thus, 3,4-dihydroxyphenylethylamine had a more energetic HOMO than the monophenolic derivatives, and 3,4,5-trihydroxyphenylethylamine had the highest HOMO energy of the phenolic amines. Highest HOMO 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 HOMO of the series. The second highest

TABLE 1

ELECTRONIC CONFIGURATION OF PHENLETHYLAMINES

Compound	HOMO*	Highest Free Valence	Position	Greatest Negative Pi Charge	Position	Greatest Frontier Electron-Density	Position	Superde-localizability†	LEMO*
Mescaline (3,4,5-Trimethoxy-phenylethylamine)	+0.5357	1.72	CH_3 at 4	−0.104	2, 6	0.5122	4	1.23	−1.12
2,3,4-Trimethoxyphenylethyl-amine	+0.5696	1.72	CH_3 at 4, 5, 6	−0.072	3	0.3960	4	1.05	−1.10
3,4-Dimethoxyphenylethyl-amine	+0.5702	1.72	CH_3 at 4	−0.074	2	0.4162	4	1.06	−1.05
4-Methoxy-3-hydroxphenyl-ethylamine	+0.6016	1.72	CH_3 at 4	−0.071	2	0.4341	4	1.02	−1.04
3-Methoxy-4-hydroxyphenyl-ethylamine	+0.6184	1.72	CH_3 at 3	−0.074	2	0.4690	4	1.05	−1.05
Methoxytyramine	+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-Trihydroxyphenylethyl-amine	+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

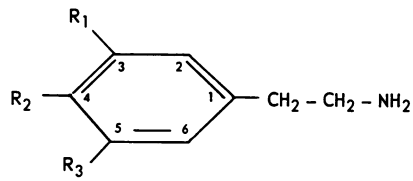
* Expressed in β units so that psilocin is a better electron donor and a poorer acceptor than phenylethylamine.
† Expressed in reciprocal β units; thus psilocin is a better electron donor than phenylethylamine.

TABLE 2

AMPHETAMINE DERIVATIVES: ELECTRONIC CONFIGURATION AND HALLUCINOGENIC POTENCY

Compound	Hallucinogenic activity*	HOMO†	Highest Free Valence	Position	Greatest Negative Pi Charge	Position	Greatest Frontier Electron Density	Position	Superde-localizability‡	LEMO*
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

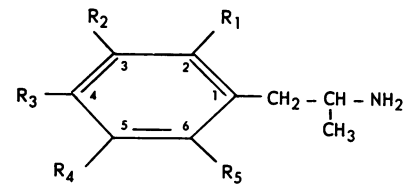
* Hallucinogenic activity values are those of Shulgin[19] and are expressed as the ratio of the effective dose of mescaline in humans (3.75 mg/kg) to the effective dose of a given drug.
† Expressed in β units so that TMA-2 is a better electron donor and poorer acceptor than TMA-3.
‡ Expressed in reciprocal β units so that TMA is a better electron donor than TMA-3.



PHENYLETHYLAMINE DERIVATIVES

COMPOUND	R_1	R_2	R_3
Dopamine	OH	OH	-
3-Methoxy-4-hydroxyphenylethylamine	CH_3O	OH	-
3,4-dimethoxyphenylethylamine	CH_3O	CH_3O	-
Mescaline	CH_3O	CH_3O	CH_3O
Tyramine	-	OH	-
Phenylethylamine	-	-	-

FIG. 1.



AMPHETAMINE DERIVATIVES

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.

value was considerably less energetic and occurred in 2,3,4-trimethoxyphenylethylamine. Progressive methoxylation also correlated with superdelocalizability, which is a function of the HOMO 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 #5 position to the #2 position (to form 2,3,4-trimethoxyphenylethylamine) results in a molecule which is devoid of hallucinogenic activity.[12] Data on the effects of 3,4-dimethoxyphenylethylamine 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 concentrations of both dopamine and tyramine in the brain can be markedly elevated in animals following treatment with monoamine oxidase inhibitors.[13, 14] Brain dopamine concentration can also be increased by the administration of its amino acid precursor, dihydroxyphenylalanine.[15] 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/gram,[16] and thus lower than brain levels of dopamine obtained after monoamine oxidase inhibition or dihydroxyphenylalanine treatment.

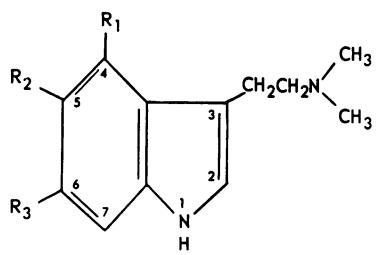
There would therefore appear to be a possible relationship between the hallucinogenic activity of phenylethylamines and the ability of these compounds to donate electrons, as indicated by the energy of the HOMO's. To test this correlation in another series, calculations were performed for a group of trimethoxyamphetamines (Fig. 2; Table 2) of widely varying hallucinogenic activity. TMA-2 (2,4,5-trimethoxyamphetamine) and TMA (3,4,5-trimethoxyamphetamine) are, re-

spectively, about 17 times and 2 times more potent than mescaline as hallucinogens, whereas TMA-3 (4,5,6-trimethoxyamphetamine) appears to be inactive.[17] 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 HOMO energies of these three compounds which correlated with the differences in their hallucinogenic potency. Thus, TMA-2 had the most energetic HOMO, 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-trimethoxyphenylethylamine. It is, therefore, interesting that hallucinogenic potency parallels HOMO 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.[18] Calculations were performed on a series of these compounds (Fig. 3; Table 3). The energy of the HOMO was greatest for psilocin (4-hydroxy-N,N-dimethyl tryptamine) and next highest for 6-hydroxy-N,N-diethyl, or dimethyltryptamine. (The molecular orbital calculations used in this study do not distinguish between N,N-dimethyl-, or N,N-diethyltryptamines.) 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,[19] and 6-hydroxy-N, N-diethyltryptamine is next most effective.[20] The administration of N,N-dimethyltryptamine or N,N-diethyltryptamine does produce hallucinogenic effects,[18] 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.[21–25]

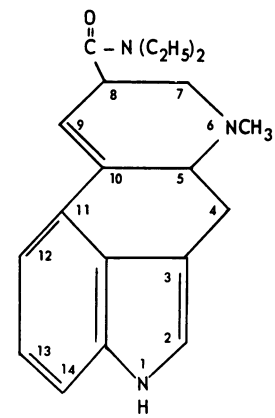
There appears, therefore, to be an excellent correlation between hallucinogenicity of the tryptamine derivatives and the energy of their HOMO. Superdelocaliz-



DIMETHYLTRYPTAMINE DERIVATIVES

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.



LYSERGIC ACID DIETHYLAMIDE

FIG. 4.

TABLE 3

TRYPTAMINE DERIVATIVES: ELECTRONIC CONFIGURATION AND HALLUCINOGENIC POTENCY

Compound	Hallucinogenic activity*	HOMO†	Highest Free Valence Position		Largest Negative Pi Charge	Position	Greatest Frontier Electron Density	Position	Superde-localizability‡	LEMO§
Psilocin	31	0.4603	1.48	O_2 at 4	−0.077	9	0.5118	2	−1.53	−0.882
6-Hydroxydiethyltryptamine	25	0.4700	1.49	O_2 at 6	−0.080	3	0.5664	2	−1.53	−0.871
Bufotenin	—§	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

* Expressed as ratio of effective dose of mescaline to effective dose of a given drug. Values for psilocin were obtained from Wolbach *et al.*,[19] and for 6-hydroxydiethyltryptamine, from Szara.[20]
† 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.
§ Weak or inactive as detailed in text.

TABLE 4

RELATIONSHIP OF HALLUCINOGENIC POTENCY IN DIFFERENT CLASSES OF DRUGS TO THE ENERGY OF THEIR HOMO

Drug	Minimum effective dose (mg/kg)	Hallucinogenic activity*	Energy of HOMO†
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.
† Expressed in β units; thus LSD is a better electron donor than TMA.
‡ As determined by Karreman *et al.*[28]

TABLE 5

TRYPTAMINE DERIVATIVES WITH INCREASED HOMO ENERGY

Compound	HOMO*	LEMO*	Greatest Frontier Electron Density	Position	Superde-localizability†	Greatest Negative Pi Charge	Position	Highest Free Valence	Position
4-Methoxypsilocin	0.4402	−0.8854	0.4753	2	1.558	−0.0822	5	1.714	CH_3 at Pos. 4
4,6-Dihydroxydimethyltryptamine	0.4231	−0.9227	0.5248	2	1.649	−0.1110	5	1.487	O_2 at Pos. 6
6-Methoxy-4-hydroxydimethyltryptamine	0.4099	−0.9257	0.5142	2	1.675	−0.1151	7	1.716	CH_3 at Pos. 6
4-Methoxy-6-hydroxydimethyltryptamine	0.4070	−0.9264	0.4972	2	1.675	−0.1156	5	1.714	CH_3 at Pos. 4
4,6-Dimethoxydimethyltryptamine	0.3954	−0.9294	0.4917	2	1.701	−0.1187	7	1.716	CH_3 at Pos. 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.

ability, a function of the HOMO 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.

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. 4) 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. Karreman *et al.*[5] calculated the HOMO energy for the complete LSD molecule and obtained a value of 0.218 β units, indicating an HOMO far more energetic than any of the compounds examined in this study.

It is possible that the very energetic HOMO value for LSD reported by Karreman *et al.*[5] may have been due simply to the use of different parameter values than those employed in the present study. To examine this possibility, HOMO and LEMO values for indole-acetic acid, catechol, the indole portion of reserpine, and serotonin determined by our techniques were compared with values for these compounds obtained by Karreman.[26] There was a close agreement between values for these compounds obtained by the two methods. The deviations between HOMO values obtained by our calculations and by Karreman[26] varied from 0.001 to 0.050 β units, whereas the HOMO energy reported by Karreman for LSD exceeds that of psilocin, the best electron donor and most potent hallucinogen examined here, by -0.242 β units. Thus, it would appear that the extremely energetic HOMO for LSD reported by Karreman *et al.*[5] is not simply an artifact of parameter selection.

As with all the tryptamine derivatives examined, the region of highest frontier electron density in LSD is at the #2 carbon atom. The position of the 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 #2 carbon should be critical for this activity. It is, therefore, interesting to note that 2-Brom-LSD[3] and 2-oxy-LSD,[28] which contain sterically obstructing substituents at the #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 HOMO 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 HOMO 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.[27]

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 structurally 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 in presumed target areas within the brain. The amphetamine and tryptamine analogues, for which hallucinogenic efficacy and electronic configuration are reasonably well established, have a close correlation between hallucinogenic potency and HOMO energy (Table 4).

The observed relationship 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 HOMO. Thus dimethoxylated derivatives, such as 4,6-dimethoxy-N, N-dimethyl-tryptamine have the most energetic HOMO'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.[29, 30]

In proposing a mechanism for drug action, one must consider a great number of 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 3,45-trimethoxyamphetamines. The absence of correlation with pi charge distribution would tend to be inconsistent with an electrostatic attraction. Furthermore, if an electron transfer mechanism is involved, the negative correlation with energy of the lowest empty orbital would indicate that the hallucinogens do not act via electron acceptance. Thus, despite the crudeness of the theoretical and experimental data discussed here, the close relationship between HOMO energy, an index of electron donation, and the hallucinogenic potency of drugs does favor an electron donation model of drug-receptor interaction.

Summary.—Molecular orbital calculations have been made for a variety of hallucinogenic and structurally similar nonhallucinogenic analogues in the phenylethylamine, amphetamine, and tryptamine series and for LSD. There is a close correlation between the energy of the highest filled molecular orbital of compounds, an index of electron donation, and their hallucinogenic potency. On the basis of these correlations, predictions have been made of the structures of compounds that might be more potent as hallucinogens than presently available drugs.

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