XV. QUANTUM THEORY:

Discussion Led by S. H. Snyder, A. T. Shulgin
J. P. Green, and D. L. Beveridge

Snyder introduced a model designed to explain some of the seeming paradoxes in the structure-activity of the psychotomimetics. This model is first addressed to the fact that different hallucinogenic drugs of very different structures produce closely similar subjective effects. This is remarkable when one considers a drug like mescaline. Mescaline, chemically, has much more in common with amphetamine than it does with LSD; yet mescaline produces effects that are frequently indistinguishable from those of LSD. Moreover, there is other evidence that these drugs act by similar mechanisms or on similar receptors. For instance, there is cross-tolerance between compounds such as LSD and mescaline, which differ so much in structure. How, then, can these compounds conform to a single or a similar receptor site? Another question, of course, relates to the remarkable differences in psychotropic potency within groups of psychotomimetic compounds that have fairly similar structures.

Molecular Models of LSD and Psilocin

Figure 24 shows the absolute configuration of d-LSD, with the four rings labeled A, B, C, D. Snyder and Richelson (a Johns Hopkins medical student) were struck by the fact that many of the psychedelic drugs can be looked at as approximating the A, B, and C rings of LSD. They found that the psychotropic potency of a large number of psychotomimetic drugs could be predicted by their relative tendencies to approximate sterically these rings of LSD.

Figures 29 and 30 show a model of psilocin (4-hydroxydimethyltryptamine), the active ingredient of psilocybin, drawn so that the ethylamine side chain is tilted over, demonstrating that when the chain is tilted in this fashion, it can approximate the 4-hydroxyl group to which it can conceivably hydrogen bond, resembling ring C of LSD. While psilocin is highly active, bufotenin, which differs from psilocin only in the presence of the hydroxyl group at CH-5 rather than CH-4, is inactive. Its consequent inability to approximate the C ring of LSD may be related to its lack of potency, a factor that could also explain the lack of psychotropic activity of 6-hydroxydimethyltryptamine.

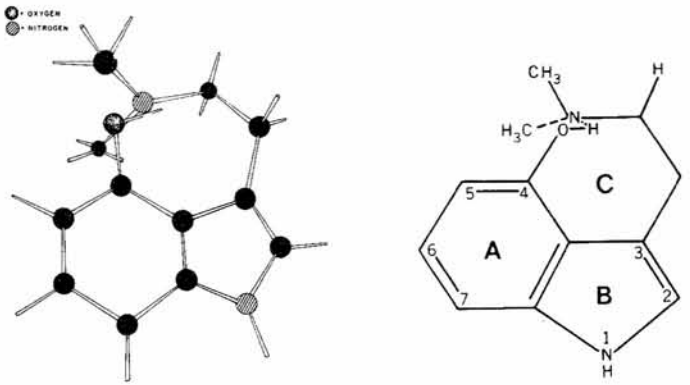


Figure 29. 4-hydroxy-N,N-dimethyltryptamine (psilocin).

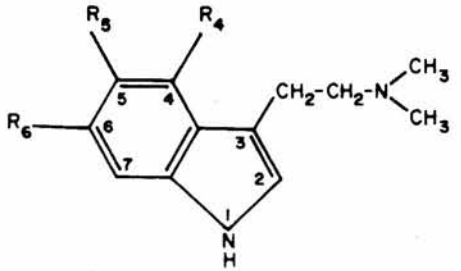


Figure 30. N,N-dimethylated tryptamine derivatives:

Compound	R_4	R_5	R_6
Dimethyltryptamine	H	H	H
Bufotenin	H	OH	H
6-hydroxy-N,N-dimethyltryptamine	H	H	OH
Psilocin (4-hydroxy-N,N-dimethyltryptamine)	OH	H	H

The suggestion was made that in the area of the receptor there may be a relatively nonpolar grouping. More specifically, the fact that the partition coefficient of these substances parallels their activity suggests that there may be a substance, a lipid, or some relatively nonaqueous medium, near or surrounding a receptor. Shulgin mentioned that partition coefficients of the 4, 5, 6, and 7-hydroxy indoles between water and oil support this comment. The 7, 6, and 5 are all at a ratio of about 2:1, the 4 is about 12:1, all in favor of the lipid.

A comment was made that it would seem to be reasonable to rotate the side chain, put the nitrogen up in the LSD-like position, and begin to form a D ring with the methyl group already in place. Snyder replied that Kier (1968) had made calculations for the preferred confor-

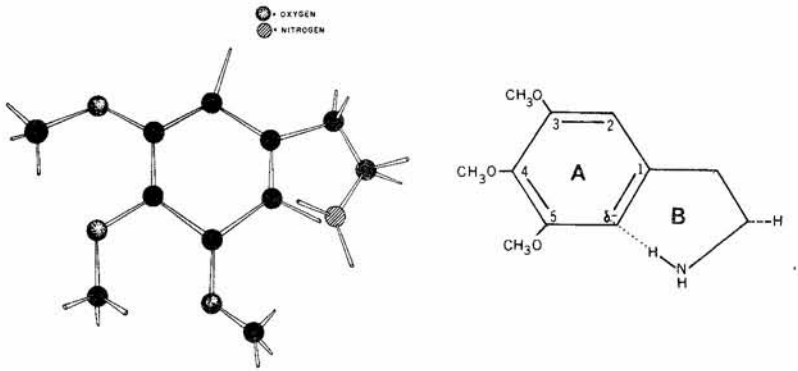


Figure 31. 3,4,5-trimethoxyphenylethylamine (mescaline).

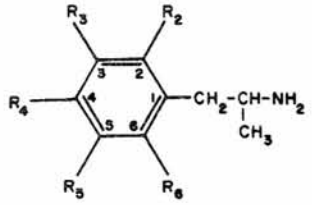
mation of 5-HT, and on this basis he feels that something of this type would be a preferred conformation for 5-HT with the 5-hydroxyl group.

Phenylethylamine Derivatives

Snyder next presented a model of mescaline (Figure 31). Although this compound is active, it is fairly weak. However, when one considers possible steric reasons why this conformation might approximate the same kind of receptor that indoles and LSD do, one might postulate that the side chain could swing down and in a sense approximate the A or B rings, that is, give an indole structure. This idea is of course not original and has been speculated upon for many years.

Amphetamines and Mescaline

When we look at the amphetamine molecules, things become more complicated and more interesting. Figure 32 gives a summary of some of the structures that Shulgin has developed. Let us consider the 3,4,5, the 3,4,5, and the 2,3,4 substituted compounds. It is difficult to say exactly what is remarkably different chemically about these groups, yet their psychotropic potency varies markedly. The 3,4,5 substitution yields a compound (TMA) that is twice as potent as mescaline. The 2,4,5 substitution (TMA-2), on the other hand, escalates to a level of potency 20 times that of mescaline, while merely switching over to the 2,3,4 position (TMA-3) gives a compound that appears to be inactive as a psychedelic drug. As has already been mentioned, Mitoma (personal



AMPHETAMINE DERIVATIVES

COMPOUND	R_2	R_3	R_4	R_5	R_6
TMA	H	CH_3O	CH_3O	CH_3O	H
TMA-2	CH_3O	H	CH_3O	CH_3O	H
TMA-3	CH_3O	CH_3O	CH_3O	H	H
TMA-4	CH_3O	CH_3O	H	CH_3O	H
TMA-5	CH_3O	CH_3O	H	H	CH_3O
TMA-6	CH_3O	H	CH_3O	H	CH_3O
DOM	CH_3O	H	CH_3	CH_3O	H
DOET	CH_3O	H	CH_3CH_2	CH_3O	H
DMMDA	CH_3O	$O-CH_2-O$		CH_3O	H
DMMDA-2	CH_3O	CH_3O	$O-CH_2-O$		H
MMDA	H	$O-CH_2-O$		CH_3O	H
MMDA-2	H	$O-CH_2-O$		H	CH_3O
MMDA-3a	CH_3O	$O-CH_2-O$		H	H
MDA	H	$O-CH_2-O$		H	H
DMA	CH_3O	H	H	CH_3O	H

Figure 32. Chart of amphetamines.

communication to Snyder) has synthesized radioactive 2,4,5 and 2,3,4 trimethoxyamphetamines and has examined their metabolism by liver microsomes, their excretion rate, their disappearance from the body, and their entry into the brain in rats, and he can find no difference between these two compounds (the most active and the least active). This suggests that it is not metabolic difference alone that accounts for the difference in psychotropic potency. What other possibilities are there?

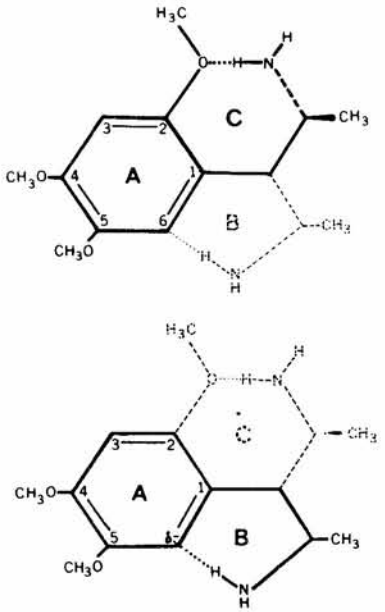


Figure 33. 2,4,5-trimethoxyamphetamine (TMA-2).

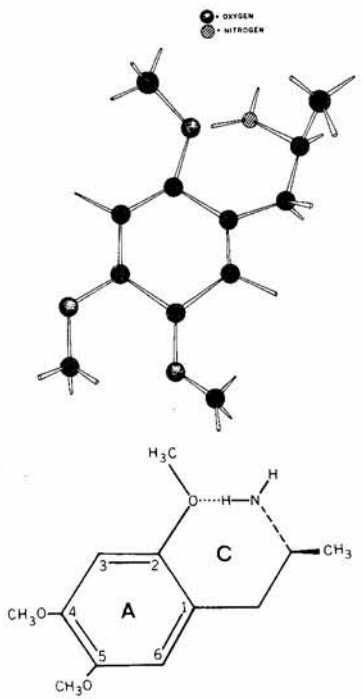


Figure 34. 2,4,5-trimethoxyamphetamine (TMA-2). Model.

Figure 33 is a schematic drawing of the most potent of these, 2,4,5-trimethoxyamphetamine (TMA-2). In one part of the figure this is drawn with the side chain rotated down to approximate the indole structure, as shown before with mescaline.

Another interesting possibility is presented if the side chain is rotated to approximate something resembling the C ring of LSD. In this case there is a possibility of intramolecular hydrogen bonding to the oxygen of the 2-methoxy group, which would constitute a stabilizing force for this particular type of conformation. Figure 34 shows a molecular model of the C ring conformation illustrated in Figure 33. There obviously could not be a C ring and a B ring simultaneously, but they could exist at different times and in different situations so that the A, B, C conformation would be approximated. This suggests that the presence of a 2-methoxy substituent should enhance psychotropic activity. As Shulgin stated, a methoxy at the 2 position in general enhances potency of these compounds. However, in order to hydrogen bond to the

side chain amine, the methoxy at the 2 position should be able to approximate an orientation in the plane or the ring. In what situation could it fail to assume this particular conformation? A methoxy at the adjacent 3 position would provide steric hindrance so that there would be a lesser tendency for the methoxy at the 2 position to assume the exact position necessary to obtain the C-ring configuration. If there were no hydrogens on the nitrogen, then there would be no possibility of forming a hydrogen bond with the methoxy at position 2 so that psychotropic activity should diminish. This prediction is supported by the fact that mescaline analogs lose activity if the nitrogen is methylated.

In 2,3,4-trimethoxyamphetamine (TMA-3), the 3-methoxy group prevents the required rotation of the 2 group, making hydrogen bonding with the side chain amine less probable and accounting for the very low psychotropic activity of this isomer. This raises the question, could there be a situation in which there is a 3 substitution where the 3 substitution would not interfere with the capacity of the 2-methoxy to approximate a side chain in this way? Shulgin has made the 2-methoxy,3,4-methylenedioxy compound (MMDA-3a) where there is substitution at the same three places, but the group on the 3 position is bound to the 4 position by the methylenedioxy bridge; in this compound there would no longer be steric hindrance for the 2-methoxy to assume whatever would be its optional position for interaction with the side chain amine to mimic ring C of LSD. Therefore, although 2,3,4-trimethoxyamphetamine is inactive, we predict that MMDA-3a should be quite active. Figure 35 shows this compound, which is indeed highly active. This is interesting; however, the prolific syntheses of Shulgin continue.

Figure 36 shows what happens if there are four substitutions on the ring. In this molecule called DMMDA there is a 2-methoxy and a 3,4 substitution, but again there is the methylenedioxy bridge between the substituents at positions 3 and 4. We would predict that this would be potent.

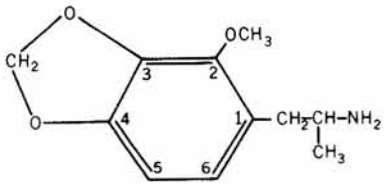


Figure 35. 2-methoxy-3,4-methylenedioxyamphetamine (MMDA-3a).

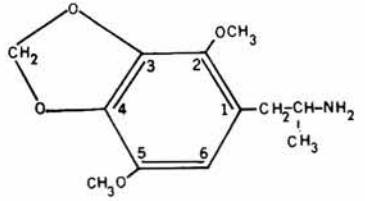


Figure 36. 2,5-dimethoxy-3,4-methylenedioxyamphetamine (DMMDA).

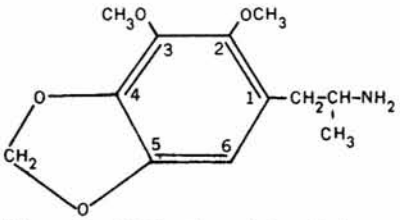


Figure 37. 2,3-dimethoxy-4,5-methylenedioxyamphetamine (DMMDA-2).

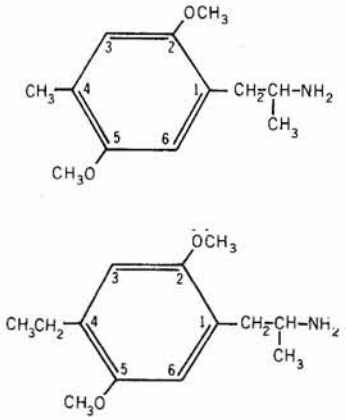


Figure 38. *Upper*: 2,5-dimethoxy-4-methylamphetamine (DOM). *Lower*: 2,5-dimethoxy-4-ethylamphetamine (DOET).

Figure 37 shows an isomer of this compound called DMMDA-2 in which the methylenedioxy bridge is between the 4 and 5 group. One would predict that because the freely rotating methoxy group at position 3 prevents the 2-methoxy from hydrogen bonding to the side chain amine, this compound would be less active; as predicted, DMMDA-2 is much less active than DMMDA.

Figure 38 shows DOM (2,5-dimethoxy-4-methylamphetamine) and DOET (2,5-dimethoxy-4-ethylamphetamine; DOET is the ethyl analog, DOM is the methyl analog). These are 2,4,5-substituted compounds resembling 2,4,5-trimethoxyamphetamine (TMA-2), the difference being that instead of a 4-methoxy group there is a methyl or ethyl group in the 4 position. According to the model, there would be nothing to make DOM or DOET any more active than TMA-2; in fact, however, DOM and DOET are 3 to 5 times more potent than the 2,4,5-trimethoxy molecule (TMA-2). This discrepancy probably occurs because a methyl or ethyl group cannot be demethylated as can a methoxy, and demethoxylation is a major mode of metabolism of the methoxyamphetamine compounds.

The one point of data that is not explained by this model would be the potency of the 4-methoxyamphetamine. This indicates that there are probably other considerations having to do with this part of the ring that are of considerable importance.

In Vivo Tests – Rat and Squirrel Monkey

Table 5 summarizes predictions for psychotropic potency of trimethoxyamphetamines and known activity of these drugs in man, monkey, and rat. The human data are largely Shulgin's (1969); the studies

TABLE 5
Psychedelic Drugs
Structure-Activity of
Trimethoxyamphetamines

Efficacy	Steric Model	Man	Monkey	Rat
Potent	2,4,5-TMA	2,4,5-TMA(17)*	2,4,5-TMA(5.4)	2,4,5-TMA(7.2_u) (4.0_s)†
	2,4,6-TMA	2,3,6-TMA(13)	2,4,6-TMA(3.2)	3,4,5-TMA(4.0_u) (1.5_s)
	2,3,6-TMA	2,4,6-TMA(10)		
Weak	2,3,5-TMA	2,3,5-TMA(4)	3,4,5-TMA(1.8)	2,4,6-TMA(1.7_u) (1.0_s)
	3,4,5-TMA	3,4,5-TMA(2.2)	2,3,5-TMA(1.1)	2,3,4-TMA(1.6_u) (0_s)
	2,3,4-TMA	2,3,4-TMA(<2)	2,3,4-TMA(0.7)	

*Numbers in parentheses are psychotropic potency in mescaline units (m.u.).
†Subscripts u and s refer to data of Uyeno and Smythies, respectively.

in squirrel monkey were performed by Edward Uyeno of Stanford Research Institute. For the rat, data comes from both Smythies and Uyeno. The monkey tests consist of a discrimination of sizes of circular objects in a Wisconsin General Test Apparatus. The Smythies test material has already been described (pp. 79-81). Uyeno used two types of tests in rats. One was a Lashley maze, and the other was an underwater swimming test in which the experimenters measured the latency of response to the starting gate, a task involving attention span, among other things (Uyeno, 1967).

For the trimethoxyamphetamines, if there is a substitution in the 2 position or in the 6, exactly equivalent to the 2 position, a considerable degree of potency can be expected; in fact, in man these particular compounds are quite potent. Compounds predicted to be less potent – if there is no 2-methoxy or if a 3-methoxy poses steric hindrance to the 2-methoxy group's interaction with the side chain – are indeed less psychoactive in man and monkey. The numbers in parentheses in Table 5 are potencies in mescaline units according to Shulgin.

In the squirrel monkey, of the drugs tested (and not all have been tested), the 2,4,5 and 2,4,6 are highly potent, just as in man; 3,4,5 and 2,3,5 and 2,3,4 are considerably less potent.

In the rat, the independent data of Uyeno and Smythies agree quite well, and 2,4,5 is again quite potent. The 3,4,5 molecule seems to be more potent than the 2,4,6 and the others in the second group. Here the rat differs somewhat from monkey and man. The 2,4,6, which is quite potent in man and the squirrel monkey, is somewhat less potent in the rat (Smythies et al., 1969), and the 2,3,4 is inactive in rat as in man and monkey.

The fact that there are some differences between activity in the rat and in squirrel monkey is interesting in the light of our discussions of the metabolism of amphetamine. Ellison (1966) has studied amphetamine metabolism in squirrel monkey and in man as well as in the rat; amphetamine is metabolized by man and the squirrel monkey in virtually the same manner, whereas the rat's metabolic pattern differs.

Table 6 shows the psychotropic activities for the methoxymethylenedioxyamphetamines. Relative potencies predicted by theory correspond closely to those observed by Shulgin in man.

The structure-activity relationships of the dimethoxy amphetamines are shown in Table 7. The pleasing thing about these data is that they do not represent hindsight; psychotropic activity in man was reported some time after publication of the theoretical model. Again it would be predicted that 2,5 and 2,4 dimethoxyamphetamines would be active, while 3,5 and 3,4 and 2,3 dimethoxyamphetamines would be

TABLE 6
Psychedelic Drugs
Structure-Activity of
Methoxymethylenedioxyamphetamines

Efficacy	Steric Model	Man
Potent	2,4-5-MMDA	2,4-5-MMDA(12)*
	2,3-4,5-DMMDA	2,3-4,5-DMMDA(12)
	2,3-4-MMDA	2,3-4-MMDA(10)
Weak	2,3,4-5-DMMDA	2,3,4-5-DMMDA(5)
	2-3,4-MMDA	2-3,4-MMDA(3)

*Numbers in parentheses are psychotropic potency in m.u.

TABLE 7
Psychedelic Drugs
Structure-Activity of
Dimethoxyamphetamines

Efficacy	Steric Model	Man	Rat
Potent	2,5-DMA	2,5-DMA(8)	3,4-DMA(2.0)*
	2,4-DMA	2,4-DMA(5)	
Weak	3,5-DMA	3,4-DMA(<1)	2,3-DMA(0)
	3,4-DMA		3,5-DMA(0)
	2,3-DMA		2,5-DMA(0)

*Numbers in parentheses are psychotropic potency in m.u.

expected to be weaker for the same reason. The 3,4 dimethoxyamphetamine has been tested in man, and it is in fact weaker than 2,5 and 2,4. In the rat, 3,4-dimethoxyamphetamine is active. Again there is a difference between man and rat, and 2,5-dimethoxyamphetamine, which is active in man, tends to be inactive in rat. As Smythies explained, this fits nicely with the possibilities for hydroxylation in the 4 position. In man, 4-hydroxylation is a minor pathway.

As Beveridge pointed out, for the side-chain nitrogen of the psilocin atom to engage in hydrogen bonding, the lone pair of electrons would have to be free, and this is not likely because at physiological pH the amino group is protonated. It is possible that in a nonaqueous biophase such hydrogen bonding could occur, although it seems improbable. However, there is no reason why the lone pair electrons of the oxygen of the phenolic hydroxyl group could not provide the electrons, as shown (Green, WS).

Charge-Transfer Complexes

Green commented that the earlier remarks about the π-system and charge-transfer complexes reminded him of a paper he and his associates had published a few years ago. They found that the order of activity of indoles in donating an electron to form charge-transfer complexes (Foster and Hanson, 1964) is not correlated with the energy of the highest occupied molecular orbital (HMO) but rather with superdelocalizability for an electron-donating reaction at the 3 position S_3E of the indole ring (Green and Malrieu, 1965). The π-electron density at this position (q_3) is not correlated with activity. Superdelocalizability is a second-order perturbation term employed to indicate the stabilization energy in the formation of a complex with another molecule (Fukui, 1964). (See Table 8.)

It is risky to make strong inferences from these results because the simple Hückel method is approximative, and the validity of superdelocalizability has been questioned; with regard to the latter objection, it should be added that superdelocalizability is formally similar to Wheland's localization energy and has been shown to correlate with the reactivities of some organic molecules (Fukui, 1964).

With these cautions in mind, Green suggested that the 3 position makes an unusual contribution to the stabilization energy of the charge-transfer complex. The early suggestion (Szent-Gyorgyi et al., 1961) that

TABLE 8
Charge-Transfer Complexes and
Some Quantum Chemical Calculations
[Green and Malrieu, 1965]

Indole	Max. c-t band* ($cm^{-1} \times 10^{-3}$)	HMO	q_3	S_3E
2,3-Dimethyl	15.15	0.443	1.142	1.812
1,2-Dimethyl	16.53	0.493	1.225	1.680
2,5-Dimethyl	17.32	0.504	1.223	1.652
2-Methyl	18.52	0.507	1.220	1.640
3-Methyl	19.01	0.476	1.089	1.576
1-Methyl	19.05	0.519	1.175	1.510
Unsubstituted Indole	19.92	0.534	1.170	1.466

*These numbers, which appear in graphical form (Foster and Hanson, 1964), were sent to us by Foster who concluded on reexamination of his results that indole is the weakest donor in this series and not, as stated in the original paper, 1-methylindole.

either the 2 or 3 position of the indole ring (or both) was engaging in a local charge-transfer interaction receives support from these calculations to the extent that they suggest a somewhat localized π interaction. Another implication of this work is that the molecules may not be associated plane-to-plane but may be oriented toward the 3 position. Subsequent nuclear magnetic resonance (NMR) studies of charge-transfer complexes of indoles (Foster and Fyfe, 1966) support the idea of a somewhat localized complex.

It is usually overlooked that early in his studies of these complexes Mulliken (1952) wrote that "Charge-transfer forces may well also be important in heterogeneous systems and ... may afford new possibilities in understanding intermolecular interactions in biological systems." These complexes are readily formed when a donor and acceptor are mixed; they are interactions of low energy and readily reversible. To someone who has worked with tissues, the analogies are obvious: for example, the action of 5-HT on the neural structure of the guinea pig ileum occurs rapidly and is reversed just by washing the tissue.

Indoles

It is difficult to attribute biological activity *solely* to the ability of a molecule to form a charge-transfer complex, for there are excellent electron donors that do not have the extraordinarily diverse and potent biological activities of indoles. Showing a correlation between a molecular

orbital calculation and activity does not necessarily establish a mechanism, because the demonstrated correlation can be internally correlated with yet another reactivity index or another related or unrelated characteristic of the molecule (as shown below); in other words, the relationship could be fortuitous. Nevertheless, it is worth considering that the ability of indoles to form charge-transfer complexes is biologically significant in that it permits the indoles to complex with receptor, after which all the nuances of electronic structure of the molecule and its geometry determine activity.

Schmitt asked if the indoles are stacked to minimize the energy as in the aromatic compounds that the E. I. DuPont company synthesized to reduce resistance in films by 8 or 10 orders of magnitude. Green replied that he did not think an indole would stack with an indole. An electron acceptor would have to be present. In this regard, it is interesting to note that Mulliken (1952) first suggested that an electron donor on adsorption to a solid may then function as an electron acceptor. When asked if he had calculated the charge distributions by the LCAO method, Green replied that he had used the simple Hückel method, but he and his associates are now using the INDO method, which considers all valence electrons, π and σ (Pople et al., 1967).

Table 9 gives some calculations on biologically active compounds. The four 3-alkyl-substituted indoles shown in this table may be regarded as four tryptamines, reading from left to right in decreasing order of psychotomimetic activity (Snyder and Merril, 1965). Activity is correlated with HMO, as pointed out previously (Snyder and Merril, 1965), but there are numerous other correlates, including free valence (F) and adjusted free valence (a). Whether these correlates mean anything cannot be said with certainty; some can be internal correlations implicit in the method. To answer these questions, the series would have to be increased.

Molecular Orbital Energy and Psychotomimetic Potency

A series of ethyltryptamines that inhibit 5-hydroxy-tryptophan decarboxylase (Hester et al., 1964) were subjected to the same analysis. As shown in Table 10, the activity was correlated with HMO ($r = -0.909$), S_2E ($r = 0.980$) and S_7E ($r = 0.977$).

If energy of the highest occupied molecular orbital correlates with psychotomimetic potency (Table 9) and also with decarboxylase activity (Table 10), it would follow that the ability to inhibit decarboxylase should be a measure of psychotomimetic potency. There is no evidence for this (Green, WS).

TABLE 9
Reactivity Indexes of Some 3-Alkyl-Substituted Indoles

	4-Hydroxy	6-Hydroxy	5-Hydroxy	Unsubstituted
HMO	0.404	0.424	0.461	0.479
q_2	1.041	1.039	1.026	1.025
S_2E	1.346	1.352	1.242	1.238
F_2	0.475	0.476	0.472	0.471
a_2	0.601	0.525	0.522	0.521
S_3E	1.568	1.564	1.554	1.514
q_5	1.103	1.078	0.982	1.041
S_5E	1.222	1.068	0.974	0.980
S_7E	1.300	1.296	1.076	1.062
q_9	1.099	1.087	1.065	1.067
F_9(or a_9)	0.129	0.122	0.115	0.115

Only π electrons are considered. The Hückel method was used. The 3 substitutent is regarded as a methyl group; a hyperconjugative-inductive model was used. [Green, 1967; see also Snyder and Merril, 1965]

TABLE 10
Correlations Between Potency of Inhibitors
of 5-Hydroxytryptophan Decarboxylase [Hester et al., 1964]
and Some Quantum Chemical Calculations
[Kang and Green, 1969]

3-(2-aminobutyl)-Indoles	Activity (Percent Inhibition at 10^{-2} m)	HMO	S_2E	S_7E
6-NH_2	100	0.339	1.496	1.614
6-Methoxy	58	0.417	1.362	1.318
6-Hydroxy	58	0.424	1.352	1.296
1,2-Dimethyl	14	0.427	1.228	1.082
2-Methyl	13	0,450	1.228	1.030
5-Methoxy	7	0.458	1.242	1.078
2,7-Dimethyl	6	0.437	1.226	1.048
1-Methyl	0	0.449	1.236	1.082
7-Methyl	0	0.461	1.236	1.050
6-F	0	0.480	0.230	1.056
Unsubstituted	0	0.479	1.236	1.062
(Correlation coefficient)		(−0.909)	(0.980)	(0.977)

Green said his thought was that HMO cannot be *the* correlate. There must be other characteristics of the molecule that determine activity, and some of the possibilities are shown in Table 9. The HMO, which is indicative of the ability to donate electrons from the whole π system, may be a property of indoles that is important to all the biological activities of these compounds and may be contributing to its affinity for receptors. But for each series of compounds in each biological system, the determinants of potency are more likely to be specific and atom-localized characteristics of the molecules rather than a property of the whole ring.

Steric Interpretation

To illustrate these points, Green presented the results of work on a series of tryptamines that stimulate contraction of the stomach strip of the rat (Figure 39). The biological activities were published by Vane (1959); resonance constants were calculated by the method described by Swain and Upton (1968). The relative activities of these indolealkylamines on the stomach strip decrease in the order 5-hydroxy, 5-methoxy,

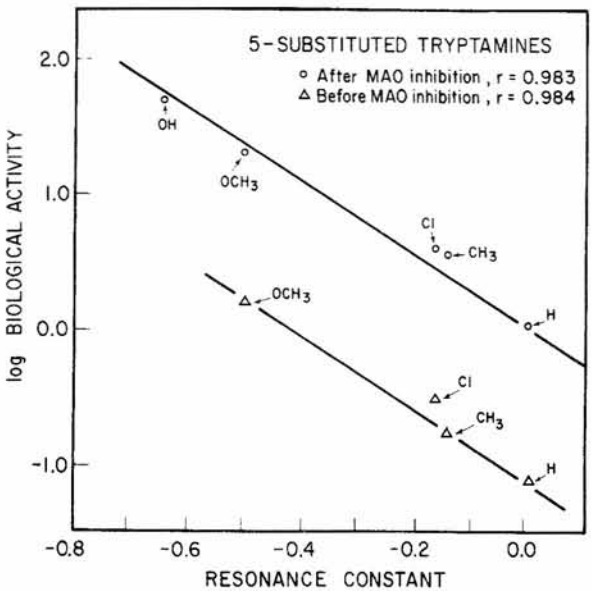


Figure 39. The correlation between contractile activity on the isolated stomach of 5-substituted tryptamines and resonance constants. [Kang and Green, 1969] Biological activity from Vane [1959].

5-chloro, 5-methyl, and the unsubstituted derivative. The order of activities was not related to the ionization constants of the primary amino group or to partition coefficients. Activity was, however, correlated linearly with the resonance constants ($r = -0.983$), with biological activity increasing with decreasing resonance constants. A similar correlation was found with α-methyltryptamines (Kang and Green, 1969a). These results imply that high electron density at an active site or sites is associated with biological activity. Which atomic site or sites are implicated is not clear from this work. It is almost certainly not the ring nitrogen because isosters lacking this atom (e.g., indenes and benzothiophenes) are active.

These results simply emphasize the importance of electronic factors in biological activity. This may seem to be a gratuitous statement, but the thought appears to need affirmation because most interpretations of the activities of congeric series like those shown in Table 10 focus almost exclusively on steric considerations. It is common, for example, to attribute the high potency of 5-hydroxytryptamine (relative to, say, tryptamine or 5-methoxytryptamine) to the ability of the hydroxy group to form hydrogen bonds with the receptor – a steric interpretation. And the greater potency of the 5-hydroxy derivative relative to the 4- and 6-hydroxy derivatives is attributed to better fit between the hydroxyl group on the 5-position and the receptor. What the results on Figure 39 suggest is that the 5-hydroxy group may not react with the receptor at all. Rather this group at that position could confer high activity on the molecule because it influences the electron system of the whole molecule and/or because it influences one or more atoms on the molecule. Examination of Tables 9 and 10 shows how significant are the effects of a substituent on an atom far removed from the substituent.

Resonance Constants and Their Limitations

The use of resonance constants or other Hammett (1940) constants has two limitations in this kind of work. First, only molecules substituted on the same position (e.g., the 5 position) can be compared. Second, the results do not suggest the atom or atoms at which the electronic effects are being manifested. As is implicit in Tables 8 through 10, molecular orbital calculations do not have these limitations. Green's laboratory analyzed the biological results of Vane (1959) by the INDO method, which considers all valence electrons (Pople et al., 1967) and which has been shown to account for many properties of large organic molecules. Figure 40 shows the activity of a series of tryptamines in

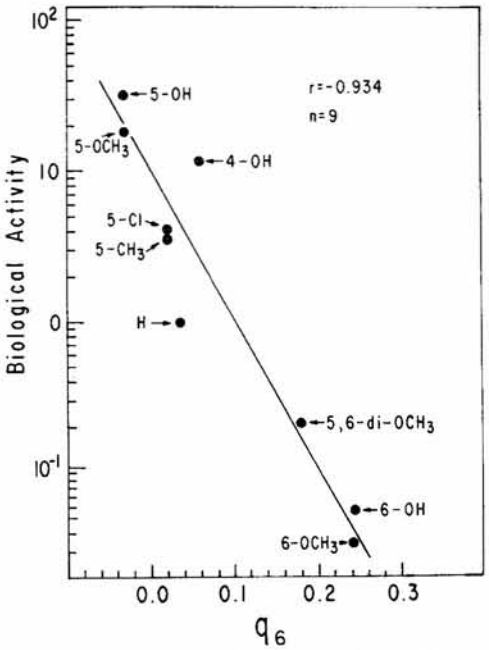


Figure 40. The correlation of contractile activity on the isolated stomach strip of 5-substituted tryptamines with their net charge at the 6 position. Calculations were done with the INDO method by Kang, Beveridge, and Green.

causing contraction of the stomach strip correlated with the net charge at the 6 position; the more negative that carbon, the more potent the congener in this series (Kang, Beveridge, and Green, in preparation). This relationship is not grasped immediately on examining Vane's original paper; the only simple generality that heretofore emerged from the empiric structure-activity study was that an amino group on the side chain is necessary for activity. These studies suggest obvious and testable hypotheses on the nature of the interaction between the tryptamines and the stomach receptor and even suggest some tentative hints of what kinds of groups may be part of the receptor. The relationship may also have predictive value. If the relationship is valid, the 4,7-dihydroxytryptamine and 7-hydroxytryptamine would be even more potent than 5-hydroxytryptamine. Perhaps more important, the relationship may show that electronic factors as well as steric factors need to be considered, that a carbon atom on a ring may be important even though it is conventionally represented only as a pair of intersecting lines, that functional groups may not be the only site of biological activity of a compound, and that an aromatic ring does not necessarily react by hydrophobic bonding.

Conclusions as to Interactions

In emphasizing the importance of electronic considerations, Green stated that he did not intend to minimize the importance of steric factors. A substance needs the appropriate geometry to fit a receptor, quite independently of electronic considerations. Further, steric factors power-

fully influence interactions that are totally electronic, as has been shown in charge-transfer complexes where the introduction into a ring of a group larger than methyl lessens the ability of a compound to function as a donor, even though the substituent increases the electron density of the ring (see Foster and Fyfe, 1966).