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Steric and Electronic Relationships among Some Hallucinogenic Compounds*

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Abstract. Stereochemical considerations and total valence electron calculations suggest congruities among the ostensibly dissimilar hallucinogenic compounds, D-lysergic acid diethylamide (LSD), indolealkylamines, and methoxylated amphetamines. In LSD the aromatic benzene ring A and the N-6 nitrogen are essential for hallucinogenic activity; these sites may react with the receptor. The conformations of amphetamines and indolealkylamines at the receptor are such that the aromatic benzene ring lies like ring A of LSD and the alkylamino nitrogen lies like the N-6 of LSD. Ring A may interact with the receptor by forming a π-molecular complex, as suggested by the correlation between hallucinogenic activity and energy of the highest occupied molecular orbital (E_H) of congeneric series. The N-6 nitrogen of LSD and the sterically congruent nitrogen of the other hallucinogenic compounds may react with the receptor by forming a donor acceptor complex of the n-π^* or n-σ^* type. Other portions of the hallucinogenic molecules confer a favorable E_H: these include the methoxy and hydroxyl groups of the amphetamines (and mescaline), and the indolealkylamines; and the pyrrole ring of LSD and the indolealkylamines.

D-Lysergic acid diethylamide (LSD), certain *N*,*N*-dimethyltryptamines (e.g., psilocin), and mescaline (and methoxylated amphetamines) have the same kind of central nervous system activity. They produce hallucinations in appropriate doses and show cross-tolerance, suggesting a common mechanism for their actions.[1,2] These compounds, despite their structural dissimilarities, may have common electronic and stereochemical characteristics that permit them to act on the same biological receptor.

Stereochemical correlations among these compounds have been proposed.[3,4] Their electronic structures have been calculated by the simple Hückel molecular orbital method[5–7] that considers only the π-electrons, a special shortcoming when applied to LSD, which has two rings lacking π-electrons. The results suggested that hallucinogenic activity was associated with a high energy of the highest molecular orbital. Recently, total valence electron calculations on twelve hallucinogenic methoxy amphetamines, which are qualitatively indistinct from mescaline,[8] showed that their potency in man correlates with the energy of the highest occupied molecular orbital.[9]

Comparable calculations on LSD and some hallucinogenic indolealkylamines

have been made to see what electronic characteristics are common to these compounds and the hallucinogenic amphetamines. At the same time, stereochemical analyses were carried out to see what tenable stereochemical characteristics are common to the three groups of compounds. The results of this analysis are presented here.

Methods. Total valence electron calculations on LSD and *N*,*N*-dimethyltryptamines were carried out by the INDO method (Intermediate Neglect of Differential Overlap),[10] which gives good results in the calculation of dipole moments and molecular geometries.[11-13] We calculated charge density, frontier electron density, dipole moment, total energy, and all orbital energy levels. The known stereochemical configuration of LSD[14,15] was followed in the analysis. Standard bond lengths and angles were assumed in generating cartesian coordinates of the molecules. Calculations were carried out on the protonated amines; for comparison, the free base of LSD, 4-hydroxy-*N*,*N*-dimethyltryptamine, and 2,5-dimethoxy-4-methylamphetamine were also used for calculations.

Results and Discussion. Stereochemical considerations: the absolute configuration of biologically active LSD is known.[14] The aromatic indole ring is planar, and the two alicyclic rings are puckered (Fig. 1). The asymmetric

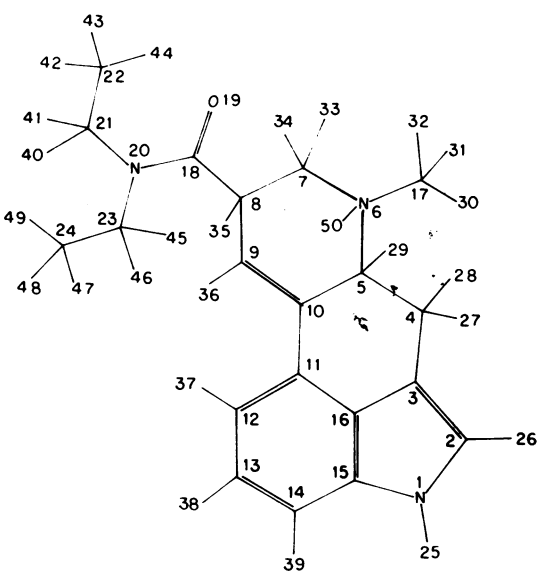

FIG. 1.—Molecular structure of LSD.

center, C-5, is above the aromatic plane, and the diethylamide group at C-8 is in the equatorial position. Although the relative geometrical assignments of N-6 and C-7 are not known, molecular models suggest that N-6 is below or near the aromatic plane and C-7 is above the plane. As the *N*-methyl group can assume the equatorial position, the long-pair electrons (or the maximum electron density) at the N-6 nitrogen are below the aromatic plane. If the N-6 nitrogen reacts with the receptor, it is most probable that the receptor, or a portion of it, is below the LSD plane.

The interaction between N-6 and the receptor may be a donor–acceptor complex (of the n-π^* or n-σ^* type) or an electrostatic interaction including hydrogen bonding. If the interaction were electrostatic, the L-form of LSD might have biological activity since the charge on the nitrogen is spread. In a donor–acceptor complex, the lone-pair electrons of the D-form will be in proximity with the acceptor, while the lone-pair electrons of the L-form will be above the plane. The inactivity of the L-form is in accord with a donor–acceptor interaction.

Amphetamines and tryptamines have freely rotating alkylamino groups. As the rotational energy barrier is small, and the preferred conformations of the free molecules are not necessarily the same as those of the molecules after interactions with the receptor, the following preferred conformations of the alkylamino groups of amphetamines and tryptamines at the receptor site are proposed to meet the requirement of a conformational adaptability similar to that of LSD.

In amphetamines (Fig. 2), C2-C1-C7-C8 is *trans* with C-8 being 0.3 Å above the aromatic plane, and C1-C7-C8-N9 is *trans* with N-9 being 0.4 Å below the plane. In tryptamines (Fig. 3) C2-C3-C10-C11 is *trans* with C-11 being 0.3 Å above the aromatic plane, and C3-C10-C11-N12 is *trans* with N-12 being 0.4 Å below the plane.

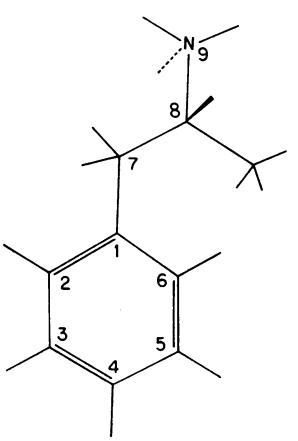

FIG. 2.—Molecular structure of amphetamine.

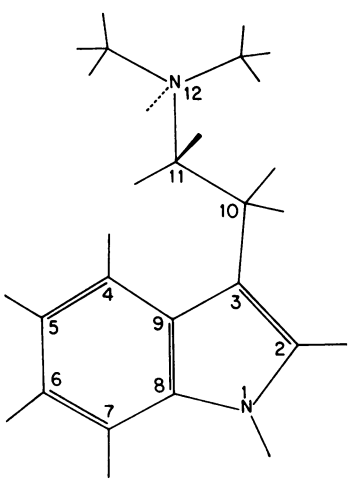

FIG. 3.—Molecular structure of *N,N*-dimethyltryptamine.

Such conformations are based on the stereochemistry of LSD. In these conformations the phenyl groups of the amphetamines and the tryptamines correspond to ring A of LSD (Fig. 4). The N-6 nitrogen of LSD corresponds to the N-9 amphetamines and the N-12 of tryptamines. The interatomic distances between the comparable carbons and nitrogens, D_{C11-N6} of LSD, D_{C1-N9} of amphetamines, and D_{C4-N12} of tryptamines are all about 3.6 Å.

This stereochemical model suggests that the necessary conditions for hallucinogenic activity are the aromatic character of ring A and an amino group in a posi-

tion like the N-6 of LSD. Other parts of the hallucinogenic molecules appear to be stereochemically gratuitous: ring B of LSD and the tryptamines, the C9–C10 double bond of LSD, the hydroxy (or methoxy) group of the tryptamines, and the methoxy groups of amphetamines and mescaline. As will be shown below, these groups are electronically important.

It has been suggested[3] that 4-hydroxy-*N*,*N*-dimethyltryptamine (psilocin) is a strong hallucinogenic compound because it can form a seven-membered ring resembling ring C (see Fig. 4) of LSD by an intramolecular hydrogen bonding between the 4-hydroxy hydrogen and tertiary amine nitrogen (Fig. 3). The activity of mescaline was attributable to the formation of ring B of LSD by a hydrogen-π interaction between the side-chain amino hydrogen and π-electrons of the benzene ring at C-2 or C-6 (Fig. 2). The activity of the amphetamines (Fig. 2) was attributable to the formation of either of two rings (ring B) by hydrogen-π interaction between the side-chain amino hydrogen and the oxygen of a methoxy group at either C-2 or C-6.

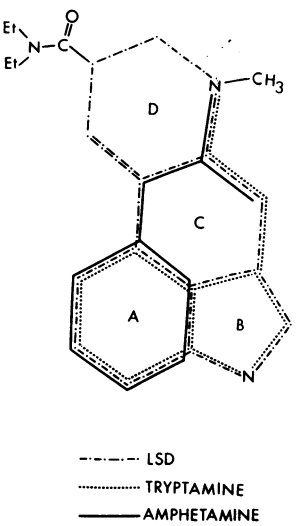

FIG. 4.—Congruence of molecular structure of LSD, tryptamine, and amphetamine.

These cyclic conformations are very unstable if they exist at all. Psilocin is protonated at physiological pH, hence it is not possible to form an intramolecular bond of the type $-O\text{-}H\cdots N(CH_3)_2$. In the protonated form an intramolecular hydrogen bond like $HO\cdots H - N^+(CH_3)_2$ – could form, but this too is unlikely, not only because the protonated form would tend to react with counterions, but because the hypothetical ring would be puckered, eight-membered, and unstable. An intramolecular cyclic conformation in mescaline by an interaction between the side-chain amino hydrogen and the π-electrons at C-2 or C-6 of the benzene ring differs from ring B in being six-membered, puckered, and nonaromatic.

According to another stereochemical analysis,[4] amphetamines exist in such a conformation that the dihedral angel $\theta_{2\text{-}1\text{-}7\text{-}8}$ is $\pm 90°$ and $\theta_{1\text{-}7\text{-}9\text{-}8}$ is 180°; a similar conformation of the *N*,*N*-dimethyltryptamines was proposed, $\theta_{2\text{-}3\text{-}10\text{-}11}$ offered as $\pm 90°$ and $\theta_{3\text{-}10\text{-}11\text{-}12}$ as 180°. Although each is a stable conformer, neither shows congruence with LSD. Calculations based on the atomic coordinates of Chothia and Pauling[4] reveal that the alkyl-ammonium nitrogens in the amphetamines and the *N*,*N*-dimethyltryptamines are 1.1 and 1.7 Å, respectively, away from N-6 of LSD. Furthermore, the alkyl-ammonium nitrogens of the amphetamines and *N*,*N*-dimethyltryptamines are located 1.45 Å above (or below) the aromatic plane whereas N-6 of LSD is 0.7 Å above the plane. In addition, the incoming protons on the nitrogen are differently oriented from the analogous proton in LSD.

Electronic considerations: among the *N*,*N*-dimethyltryptamines, hallucinogenic activity correlates with energy of the highest occupied molecular orbital

(Table 1), as previously demonstrated by Hückel π-electron calculations[6,7] and, recently, in a series of hallucinogenic amphetamines by INDO calculations.[9] The *N,N*-dimethyltryptamine derivatives have higher E_H than the corresponding tryptamine derivatives (Table 1), a difference that may account in part for the relative inactivity of the tryptamines.

TABLE 1. *Electronic characteristics of some hallucinogens and related compounds.*

Compound	Potency in man (mescaline units)	(E_H, atomic units) Free base	Protonated form	N-6 Electronic density of high-lying orbitals
LSD	4500–9275[2]	−0.3469	−0.4745	0.7511
N,N-dimethyltryptamines				
4-OH	32[16]	−0.3399	−0.4493	0.7111
6-OH	25[17]		−0.4533	
5-OH	weak or inactive[6]		−0.4666	
Unsubstituted	weak or inactive[6]		−0.4745	
Tryptamines	no activity			
4-OH		−0.3415	−0.4582	
6-OH			−0.4583	
5-OH			−0.4735	
Unsubstituted			−0.4810	
2,5-dimethoxy-4-methyl-amphetamine	80[8]	−0.3776	−0.4929	0.6584

E_H alone did not correlate with hallucinogenic activity among structurally different hallucinogens, namely LSD, amphetamines, and tryptamines (Table 1). The lack of correlation among the different series and the relatively low activity of the amphetamines, and especially of the *N,N*-dimethyltryptamines, may rest on the fact that only a small portion of the postulated conformers exist at the receptor site. Also, a correlation between one electronic characteristic, e.g., E_H, and hallucinogenic activity of different congeneric series may be too much to expect in view of the numerous interactions[7] that occur between swallowing a hallucinogen and observing an effect: absorption, excretion, catabolism, binding to plasma proteins, penetration of the blood–brain barrier, affinity for the receptor, and intrinsic activity.

The requirement of a high E_H for hallucinogenic activity explains the need for those portions of the molecules that are sterically unimportant: the pyrrole portion of LSD and psilocin; the methoxy and hydroxy groups of the amphetamines, mescaline, and the indolealkylamines; and the C9–C10 double bond of LSD. All these groups help to confer on the molecule a high E_H.

Testable predictions may be made from these inferences as they have been for the hallucinogenic amphetamines.[9] If the suggested steric and electronic requirements for hallucinogenic activity of the *N,N*-dimethyltryptamines are correct, at least five untested derivatives should have greater hallucinogenic activity than the 4-hydroxy derivative, the most potent derivative known. The hallucinogenic activities of these untested *N,N*-dimethyltryptamines would be 4-amino- = 5,7-dimethoxy- > 5,6-dimethoxy- = 5,7-dihydroxy- = 5-dimethylamino- > 4-hydroxy. The 7-hydroxy derivative would be equally as potent as the 6-hydroxy derivative. This analysis also suggests (see Figs. 2 and 3)

that 2-amino-1,2,3,4-tetrahydronaphthalenes bearing electron-donating groups (such as methoxy groups) on the aromatic ring would be hallucinogenic; as rigid structures with the amino group appropriately fixed, these compounds should be more potent hallucinogens than mescaline and the methoxylated amphetamines.

Abbreviations: LSD, D-lysergic acid diethylamide; INDO, Intermediate Neglect of Differential Overlap.

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