ON THE CONFORMATIONS OF HALLUCINOGENIC MOLECULES AND THEIR CORRELATION

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Communicated by Linus Pauling, June 13, 1969

Abstract.—There are only a few possible conformations of D-lysergic acid diethylamide and hallucinogenic derivatives of tryptamine and phenylethylamine. Of these possible conformations there is a high structural correlation among the probable conformations of active hallucinogenic molecules and between these conformations and the known conformations of several central nervous system transmitter molecules.

Both the subjective impressions of the hallucinatory effect of compounds related to lysergic acid, tryptamine, and phenylethylamine[1] and the cross tolerance that occurs between D-lysergic acid diethylamide, psilocybin, and mescaline[2, 3] imply a common mechanism for their action. A molecule's properties are intimately related to its structure; in this paper we propose probable conformations for these hallucinogenic molecules, and correlate these conformations with each other and with those of nerve transmitter molecules.

In the following discussion we are assuming that normal stereochemical rules apply, that is, that the interatomic distances and angles of bonded atoms and lower limits of non-bonded distances are known. In the first instance free rotation around single bonds is assumed. If these interatomic distances and relative bond directions are accepted, any structural conformation can be discussed in terms of the torsion angles of the bond directions.[4]

All known or suspected central nervous system transmitters are alkyl amines, as are most known drugs affecting the central nervous system. At the pH of the brain, the nitrogen atom of these molecules is charged. The pKb of N7 of lysergic acid diethylamide (LSD), is 7.8, that of N12 of tryptamine is 10.2, and that of N9 of 3,4-dimethoxyamphetamine is 9.6.[5] The pH of blood is 7.4 and that of the brain is slightly higher.[6] The blood pH of 7.4 implies that the charged:uncharged equilibrium of LSD is 75:25. The 25 per cent uncharged molecules can pass through the blood-brain barrier and as they do so the equilibrium keeps the supply of uncharged molecules at a constant proportion. On the brain side of the barrier, the equilibrium is set up again, and more than 75 per cent of the molecules are charged and can affect the central nervous system. In the following discussion we have considered only the conformations of molecules with the relevant nitrogen atom charged, forming a quaternary ammonium.

Lysergic Acid Diethylamide.—By several orders of magnitude, lysergic acid diethylamide is the most potent hallucinogenic agent known.[1] Doses of about 5 parts in 10^{10} body weight cause manifold changes in the thought processes. Rings A and B of LSD (Fig. 1*a*) form an aromatic system and the atoms are coplanar. Ring C is subject to considerable strain, as the aromatic system forces atoms C11, C13, C14, C15, and C6 to be approximately coplanar. C12 is above

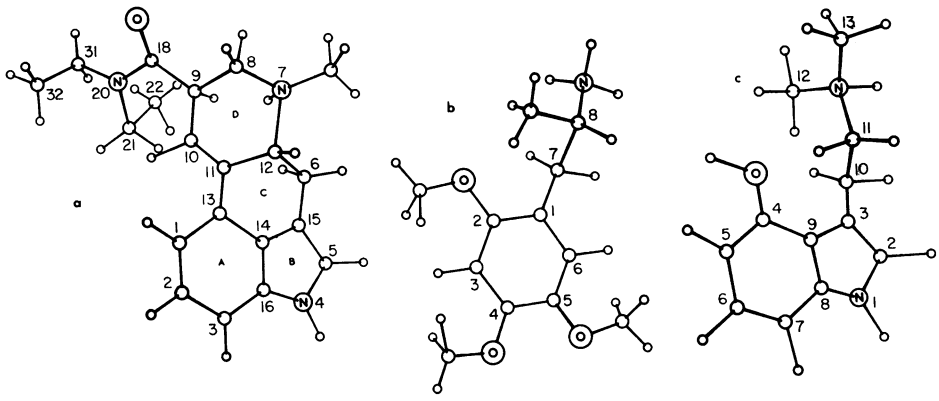

FIG. 1.—(*a*) The most probable conformation of the potent hallucinogen D-lysergic acid diethylamide. (*b*) A probable conformation of 2,4,5-trimethoxyamphetamine. (*c*) A probable conformation of 4-hydroxy-*N*,*N*-dimethyltryptamine.

the ring in the S enantiomer and below in the R enantiomer; the active D-LSD is S at C12, so this atom is above the plane of C11, C6, and the aromatic rings.[7] Excluding the rotation of three methyl groups, the conformation of LSD has five parameters. Everything else is fixed by stereochemical principles, including the position of the two ring nitrogen atoms. The three methyl group orientations are assumed to be staggered. The five parameters are (1) the position of carbon atom C8 above or below the plane of the rest of the ring (ring D in Fig. 1*a*); (2) the absolute configuration of the tetrahedral nitrogen atom N7; or the position of the methyl group C19; (3) the torsion angle O-C18-C9-C8; or the equivalent torsion angle N20-C18-C9-C8 (or the equivalents to C10 instead of C8); or the orientation of the amide group; (4, 5) the torsion angle C22-C21-N3-C14 and the torsion angle C32-C31-N3-C14; or the orientation of the ethyl groups. There are various possibilities for each of these parameters and various probabilities for each possibility. We discuss the possibilities and their probabilities in the following paragraphs.

(1) There are two possible positions for C8: (*i*) above and (*ii*) below the plane of the rest of ring D. The rest of ring D is held in one plane by the C10-C11 double bond. The absolute configuration of C9 is known[7] (S), and if the diethylamide group be equatorial rather than axial, C8 must be above the plane of the ring. This conformation is such as to separate the positive nitrogen atom N7 and the carbonyl oxygen atom by the maximum amount; if C8 be below the plane of the ring, these two atoms are brought more closely together. Evidence from studies in the synthesis of LSD suggest that the amide group is equatorial[8] and hence that C8 is above the plane, though as far as we are able to determine, no structural evidence is available to resolve this question unambiguously. We have proceeded on the basis that the amide is equatorial and C8 is above the plane of the ring.

(2) The ring nitrogen atom N7 is tetrahedral. The methyl group C19 could occupy either of the two non-ring bond tetrahedral positions. The actual location of these two positions is determined by the position of C8 discussed in (1). If C8 is below the ring, the above-ring N-bond direction is more or less axial and the below-ring N-bond direction more or less equatorial. If C8 is above the ring, the reverse is true. Substituted ter-

tiary amines in ring systems are usually equatorial. In *l*-cocaine hydrochloride, for example, the methyl on the ring nitrogen atom is equatorial.[9] Only when some other interactions affect the conformation is the amine substituent axial, as occurs in hyoscine hydrobromide,[10] where the distance of the epoxide oxygen atom on the 5-membered ring from the nitrogen atom precludes the axial position (in terms of the 6-membered ring) of the methyl group. We conclude that the methyl group is equatorial and that, if conclusion (1) is correct, it is in the position shown in Figure 1*a*.

(3) The amide group is always planar,[11] that is, C9, C18, O, N20, C21, and C31 necessarily lie in one plane because of the partial double bond character of the N20-C18 bond. In alkyl amides this plane is usually parallel to the carbon-carbon bond neighboring C18, that is, in D-LSD τ C8-C9-C10-O is 0 or $-120°$. The ethyl groups also restrict the orientation of the amide to this range. No structure of an amide connected to a ring system containing one double bond has been analyzed and the parameter cannot be determined unambiguously, but it appears from spacefilling CPK models that somewhat better packing is obtained with τ C8-C9-C18-O approximately 0°, as shown in Figure 1*a*.

(4, 5) There are three symmetric staggered conformations of the two ethyl groups on the amide nitrogen atom N20: both τ C22-C21-N20-C18 and τ C32-C31-N20-C18 = 180°, +60°, and −60°. The latter two are enantiomeric, and are equivalent except for chirality and interaction with the rest of the molecule. The first conformation is an extended $H_3C—CH_2—N—CH_2—CH_3$ chain. This extended conformation is that found in *N,N*-hexamethylene bispropionamide.[12] In LSD the completely extended conformation is impossible; τ C32-C31-N20-C18 can only be near to −60° because of steric hindrance between this ethyl group and the ring. It is unlikely that the other ethyl group is extended because of steric hindrance between the methyl group C22 and the methylene C31, and while τ C22-C21-N20-C18 = +60° appears to be possible, we prefer the symmetric conformation with τ C22-C21-N20-C18 = −60° because of its better packing and increased van der Waals stabilization.

A drawing of the most probable conformation of D-lysergic acid diethylamide is given in Figure 1*a*, and coordinates in picometers on an orthonormal coordinate system of a model of this conformation are given in Table 1.

The Methoxy Phenylethylamines and Amphetamines.—Shulgin, Sargent, and Naranjo have synthesized and tested a large number of methoxy-substituted phenylethylamines and amphetamines which have hallucinatory activity in humans.[13] These molecules all consist of a benzene ring, which is planar, substituted by a number of methoxy groups and an ethylamine or isopropylamine group (Fig. 1*b*).

TABLE 1. *Atomic coordinates in picometers of a model of the most probable conformation of* D-*lysergic acid diethylamide.*

The origin is at the center of ring A.

ATOM	X	Y	Z	ATOM	X	Y	Z
N4	53	−114	0	C17	265	495	184
C5	336	−2	0	C8	58	556	78
C15	258	115	0	C9	−25	531	−42
C13	0	138	0	C10	−55	382	−48
C1	−120	−66	0	C11	25	287	0
C2	−122	−70	0	C18	−157	610	−30
C3	0	−136	0	O	−239	660	54
C16	123	−69	0	N20	−229	616	−145
C14	123	72	0	C21	−179	552	−268
C6	273	264	0	C22	−126	669	−360
C12	155	324	71	C31	−356	683	−158
N7	175	470	72	C32	−475	589	−140

We shall begin by considering the orientation of methoxy groups. Normally, a single methoxy is in the plane of the benzene ring, as found in codeine hydrobromide dihydrate.[14] As seen in Figure 1*b*, τ C1-C2-O-CH_3 is 180°. If two methoxy groups are *ortho* to each other, the two methoxy groups would normally be in the plane of the ring but antiparallel to each other. In Figure 1*b*, τ C3-C4-O-CH_3 equals 0° and τ C4-C5-O-CH_3 equals 180°. The methoxy groups cannot be parallel to each other (τ C3-C4-O-CH_3 = 0° and τ C4-C5-O-CH_3 = 0°) because an oxygen atom is too large to accommodate a parallel *ortho* oxymethyl group. If three methoxy groups are *ortho* to each other, the two outer groups would be in the plane of the ring and antiparallel to each other. The methoxy in the middle position cannot, however, be in the plane of the ring because of the *ortho* oxygen atoms; the torsion angle must be ±90° with the methyl perpendicular to the plane of the ring. The methoxy groups are not free to rotate about either the C ring O bond or the O CH_3 bond.

In a methoxy-substituted phenylethylamine the conformation becomes slightly more complicated because of the steric hindrance of the ethylamine chain to the methoxy group at the 2 position. If there is a hydrogen atom at the 3 position, τ C1-C2-O-CH_3 would be 180°. It cannot be 0° because of steric hindrance of the ethylamine chain. If there is also a methoxy in the 3 position τ C1-C2-O-CH_3 cannot be 180° because of the ortho oxygen atom, which is too large; τ C1-C2-O-CH_3 must be +90°. Assuming the ethylamine chain to be above the plane of the ring or τ C6-C1-C7-C8 = −90° (which merely establishes an arbitrary sign convention) the C2 methoxy methyl will be below the plane of the ring (τ C1-C2-O-CH_3 = +90°) because of steric hindrance with the ethylamine chain. Otherwise the general principles are the same as for methoxy-substituted phenyl.

The ethylamine chain is normally antiplanar and perpendicular to the plane of the ring, that is, τ C6-C1-C7-C8 = −90° and τ C1-C7-C8-N1 = 180°. This is the conformation found, for example, in crystals of phenylethylamine itself,[15] dopamine hydrochloride,[16] di-iodo-L-tyrosine,[17] and the phenylalanyl part of DL-glycyl-phenylalanyl-glycine.[18] In special circumstances, such as intermolecular or possibly intramolecular hydrogen-bonding, other conformations are found. In histidine hydrochloride,[19] for example, τ C1-C7-C8-N is 71° (almost synclinal), but there are three intermolecular hydrogen bonds to the charged nitrogen atom.

When a hydroxy or methoxy group is substituted in phenylethylamine at the 2 position there is a possibility of an intramolecular hydrogen bond between the normally charged ethylamine nitrogen atom and the 2-oxygen atom. If such a bond were to form we find from building CPK space-filling models that τ C6-C1-C7-C8 is approximately −105° and τ C1-C7-C8-N is approximately −60°.

As an example of the conformation of the oxy-substituted phenylethylamines and amphetamines, we shall discuss the conformation of 2,4,5-trimethoxyamphetamine. Excluding the orientation of the methyl hydrogen atoms, the conformation of this molecule is a six-parameter problem. The parameters are (1) the torsion angle C6-C1-C7-C8; or the orientation of the ethylene chain with respect to the ring; (2) the torsion angle C1-C7-C8-N; or the orientation of the nitrogen atom with respect to the ethylene chain and the ring; (3) the absolute configuration of C8; or the position of the methyl group C9; (4, 5, 6) the orientation of the methoxy groups with respect to the ring.

Possible and probable values of these parameters are as follows:

(1) There are two possibilities of the torsion angle C6-C1-C7-C8, the other possibility being equivalent by the symmetry of the compound. These two possibilities are −90° and 0°. As discussed above, unless there are extenuating circumstances this torsion angle is 90°. In all related compounds whose conformation are known this torsion angle is between ±77° and ±102°.

(2) If τ C1-C7-C8-N is 180°, τ C1-C7-C8-C9 is ±60° (the sign would depend upon the absolute configuration) and we would expect this conformation or that with τ C1-

C7-C8-C9 $\simeq$ 180° and τ C1-C7-C8-N $\simeq \pm 60°$ to be the normal one. In phenylalanine,[2] however, we have τ C1-C7-C8-C9 $\simeq$ 59° and τ C1-C7-C8-N $\simeq$ 62°, which conformation is stabilized by hydrogen bonds. We must also include the possibility of a hydrogen bond formed to the oxygen atom in the 2 position, in which case the torsion angle is approximately −60°. If such a hydrogen bond were formed, the torsion angle H-N-C8-C7 would be +60°, and the O . . . H-N hydrogen bond linear.

(3) Hallucinogenic activity of methoxyamphetamines appears to be tested with racemic substances. There is no evidence at the moment to suggest that one enantiomer is more active than the other, though it would be valuable to test the activities of the separated enantiomers. We have indicated the R enantiomer as the more active, on the basis of its closer correlation with LSD.

(4, 5, 6) The orientations of methoxy groups relative to aromatic rings are discussed above.

We conclude that 2,4,5-methoxyamphetamine has the methoxy groups in the plane of the ring; the ethylene chain approximately normal to the plane of the ring, and the nitrogen atom antiplanar to the ring. In Figure 1*b* we depict a conformation that correlates with LSD consistent with these limits. In Table 2 there are given atomic coordinates in picometers on an orthonormal coordinate system chosen subjectively for correlation with LSD of this conformation of 2,4,5-trimethoxy-(R)-amphetamine.

For methoxy or methylene-dioxy groups substituted at other positions in the ring, the conformation can be predicted from the general rules given above. If there is no oxygen at the 2 (or 6) position, there is no possibility of intramolecular hydrogen-bonding and the ethylamine chain is expected to be antiplanar. If there is a methoxy group at the 3 position in addition to one at the 2 position, τ C1-C2-O-CH_3 must be −90° because of steric interaction with the 1-ethylamine and the 3-methoxy groups. Methylene-dioxy groups must lie in the plane of the phenyl ring.

The Tryptamines.—Tryptamines with hallucinogenic activity include the derivatives *N,N*-dimethyl, *N,N*-diethyl, 4-hydroxy *N,N*-dimethyl (psilocin), 4-phosphate *N,N*-dimethyl (psilocybin), and α methyl.[21] Psilocybin is rapidly hydrolyzed to psilocin *in vivo*.[22] As an example of this class of hallucinogens we shall discuss the conformation of psilocin, which has three structural parameters excluding hydrogen orientations: (1) the torsion angle C2-C3-C10-C11; or the position of the α-carbon atom relative to the plane of the ring system; (2) the torsion angle C3-C11-C12-N; or the position of the nitrogen atom relative to (1); (3) the torsion angle C10-C11-N-C12 or its equivalents; or the orientation of the nitrogen atom.

TABLE 2. *Atomic coordinates in picometers of a model of the conformation of 2,4,5-trimethoxyamphetamine.*

The origin is at the center of the benzene ring.

ATOM	X	Y	Z	ATOM	X	Y	Z
C1	70	121	0	NH_3	247	427	145
C2	−70	121	0	CH_3	35	317	211
C3	−140	0	0	O(2)	−142	243	0
C4	−70	−120	0	CH_3(2)	−285	223	0
C5	70	−121	0	O(4)	−142	−243	0
C6	140	0	0	CH_3(4)	−285	−223	0
C7	147	255	0	O(5)	142	−243	0
C8	173	300	145	CH_3(5)	285	−223	0

Possible and probable values of these parameters are:

(1) τ C2-C3-C10-C11 = 0°, +90° or −90°, or the position of the α-carbon atom: in the plane of the rings away from the six-membered ring or above or below it; τ = 180° (in the plane of the rings towards the six-membered ring) is impossible because of steric hindrance. Each of the three values is found in crystals of relevant compounds. In crystals of serotonin creatine sulphate, τ C2-C3-C10-C11 equals 9°.[23] This is unusual, and the conformation is stabilized by multiple intermolecular hydrogen bonds. As discussed above, in most known ring ethylamine structures τ C2-C3-C10-C11 is about ±90° with the α-carbon atom C11 above or below the plane of the ring. In L-tryptophan, for example, this torsion angle is +78°.[24] The conformation with $\tau \approx -90°$ is that which correlates most closely with the structure of D-LSD.

(2) The three staggered conformations of τ C3-C10-C11-N are ±60° and 180°. In serotonin and in most of the phenylethylamines mentioned above τ is about 180°; that is, antiplanar. This would appear to be the stable conformation unless some other inter- or intramolecular stabilizing effect is present. In histidine hydrochloride monohydrate,[19] L-tryptophane hydrochloride,[24] and L-phenylalanine hydrochloride τ C3-C10-C11-N is about ±60°.[20] In all these structures there are multiple intermolecular hydrogen bonds to the nitrogen atom. At −60° the nitrogen atom is in a position where in the case of psilocin it is possible to form an $N \ldots$ H-O hydrogen bond with the oxygen atom in the 4 position on the six-membered ring.

(3) If the N^+-04 hydrogen bond exists, τ C10-C11-N-C13 equals ±120°, corresponding to a C10-C11-N-H . . . O torsion angle of 0°, an eclipsed conformation. The hydrogen bond stabilization energy may be greater than the destabilization of the eclipsed N-C11 conformation and may fix the orientation of the nitrogen atom and the methyls in the "free" molecule. Alternatively, if an N^+-04 hydrogen bond is not formed and τ C3-C10-C11-N approaches 180°, the most stable conformation for the methyl groups on the nitrogen atom is staggered to the H atoms on C11. Many hallucinogenic tryptamines do not contain a 4-OH group so cannot have the hydrogen bonded conformation. A likely conformation of psilocin with a high correlation with the conformation of D-LSD is shown in Fig. 1*c*, and its coordinates are given in Table 3.

Correlation.—In the above paragraphs we have shown that the structure of LSD is fairly rigid, and that phenylethylamine tryptamine and derivatives contain a planar group and a flexible side chain which can take up several different conformations whose energies are not widely separated. Any one conformation relevant to a biological system would be stabilized relative to the others on interaction with an active site. In Figure 1, *b* and *c*, we show reasonable conformations for molecules representative of the hallucinogenic phenylethylamines and tryptamines. Between these conformations and that of LSD (Fig. 1*a*) there are the following correlations: (1) a charged nitrogen atom 510–570 picometers from the center and 70–140 picometers above the plane of (2) an aromatic ring

TABLE 3. *Atomic coordinates in picometers of a model of the conformation of 4-hydroxy-N,N-dimethyltryptamine.*

The origin is at the center of the six-membered ring.

ATOM	X	Y	Z	ATOM	X	Y	Z
N1	253	−114	0	C9	123	72	0
C2	336	−2	0	C10	318	257	0
C3	260	114	0	C11	303	314	145
C4	0	138	0	N	327	456	145
C5	−120	66	0	CH_3(N)	224	526	56
C6	−122	−70	0	CH_3(N)	301	514	78
C7	0	−136	0	O(4)	0	284	0
C8	123	−69	0				

system; (3) a nitrogen or oxygen atom corresponding to position 4 in LSD or position 1 in tryptamine derivatives or substituted on position 5 in phenylethylamine derivatives, and, usually, (4) a point of electron density corresponding to the 10–11 double bond in LSD, the 4-oxygen atom in tryptamine derivatives, or the 2-oxygen atom in phenylethylamine derivatives. The aromatic systems have donor character increasing in the order: methoxyphenylethylamine and amphetamines, tryptamines, LSD.[25, 26] Items (3) and (4) increase but are not essential for hallucinogenic activity.

Snyder and Richelson[27] have suggested conformations of hallucinogenic drugs and a correlation among them. We believe that some of the conformations they suggest are very unstable, if not impossible, and that therefore their correlation is unreasonable. The conformational basis of their correlation is that the flexible side chain in psilocin is hydrogen bonded to give a ring similar to ring C in LSD, and in phenylethylamines and phenylisopropylamines the side chain is hydrogen bonded to ring π electrons at C2 or C6 to mimic ring B of LSD, or hydrogen bonded to methoxy at C2 or C6 to give a ring similar to ring C in LSD. Their structures do not have charged quaternary nitrogen atoms. While Snyder and Richelson's statements about the lengths of the proposed hydrogen bonds are ambiguous, their figures appear to show impossibly short interatomic contacts and unreasonably acute angles at the hydrogen atom. The shortest observed N-O distance in a N . . . H-O hydrogen bond is about 268 picometers[28] and the minimum N . . . H-O angle is about 150°.[29] There is some controversy about the existence of hydrogen bonds to the π electrons of an aromatic system, but in all cases where such bonding has been proposed the hydrogen donating group is acidic,[28] whereas in hallucinogenic substances the nitrogen atoms are basic. While as proposed by Snyder and Richelson and discussed above it appears possible for the nitrogen atom to form a hydrogen bond to an oxygen atom at the 2-position in phenylethylamines and to the 4-position in tryptamines, the conformational correlation with LSD is higher when these bonds are not formed.

Though it is possible to propose likely conformations with high correlations for these types of hallucinogenic molecules, too little is known to be able to form a complete theory of structure-activity correlation. Many factors other than conformation affect activities, such as absorption, transport across barriers, rate of metabolism, and possible active metabolic products.

Acetylcholine, noradrenaline, and serotonin are probably nerve transmitters in the central nervous system. The above discussion of tryptamines applies to serotonin (5-hydroxytryptamine), and the correlation of its structure with LSD and phenylethylamines is the same. We think that the blockage of smooth muscle[30] and snail central nervous system serotonin receptors[31] by LSD is best seen in terms of this structural relationship.

There is a correlation between the observed crystal structure of noradrenaline[32] and the conformations discussed above that may explain the reduction in concentration of brain catecholamines by these hallucinogens.[33] There is no obvious structural correlation between acetylcholine and hallucinogens. LSD contains a quaternary nitrogen and a carbonyl group in a structural relationship

somewhat similar to that in acetylcholine.[34, 35] Phenylcholine derivatives are agonists of acetylcholine at receptors in the ganglia,[36] and phenylcholine—a quaternary nitrogen linked to an aromatic group—is similar to the conformations of hallucinogens presented above. Whether these structural similarities account for the blockage of snail central nervous system cholinergic receptors by LSD[31] or the curare-like activity of 5-hydroxytryptamine[37] and mescaline[38] requires further investigation.

We thank Mr. John Cresswell for the drawings and Miss Joan Chapman for assistance.

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