Psychedelic drugs are a class of compounds that produce a characteristic set of profound and unique changes in human perception, thought, and feeling. There are at least three structurally dissimilar classes of psychedelic drugs: the lysergic acid group, derivatives of tryptamine, and compounds related to phenylethylamine or phenylisopropylamine. Within each of these structural classes, some compounds are potent psychedelic agents while others are ineffective. Several workers have attempted to find chemical or biological properties that are unique to active psychedelic agents of differing chemical structure. Effective psychedelic drugs that have been examined elevate brain concentrations of serotonin, and central sympathetic stimulation parallels psychedelic potency. It is probable that these compounds act on the same central receptor, since cross tolerance occurs between psychedelic drugs of such diverse structures as d-lysergic acid diethylamide (LSD), psilocybin, and mescaline.

We observed a close relationship between the potency of psychedelic drugs and their electronic configuration. A theoretical model was developed that predicted the potency of psychedelic agents within a given structural class on the basis of the energy of their highest occupied molecular orbital.

Recently, in making molecular models (Dreiding-stereo models [Swisso]) of a variety of psychedelic compounds of tryptamine, phenylethylamine, and phenylisopropylamine classes, we observed that they could all approximate a unique conformation, simulating in part rings A, B, and C of LSD (Fig. 1). This report describes the conformation of a variety of psychedelic molecules,
TABLE 1. Methoxyamphetamines: Psychedelic potency and tendency to approximate the conformation of LSD.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Positions of substituents</th>
<th>Tendency to Approximate the Conformation of LSD</th>
<th>Potency (MU)</th>
<th>Potency in monkey†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMA-6</td>
<td>2,4,6</td>
<td>0 4 4.0</td>
<td>10–15‡</td>
<td>3.2</td>
</tr>
<tr>
<td>TMA-2</td>
<td>2,4,5</td>
<td>0.7 2 2.7</td>
<td>17†</td>
<td>3.4</td>
</tr>
<tr>
<td>MMDA-2</td>
<td>2,4,5</td>
<td>0.7 2 2.7</td>
<td>21†</td>
<td>—</td>
</tr>
<tr>
<td>MMDA-3a</td>
<td>2,3,4</td>
<td>0.6 2 2.6</td>
<td>18†</td>
<td>—</td>
</tr>
<tr>
<td>TMA-5</td>
<td>2,3,6</td>
<td>0 2 2.0</td>
<td>&lt;10†</td>
<td>—</td>
</tr>
<tr>
<td>TMA</td>
<td>3,4,5</td>
<td>2 2 2.0</td>
<td>2.2†</td>
<td>2.0</td>
</tr>
<tr>
<td>MMDA</td>
<td>3,4,5</td>
<td>2 2 2.0</td>
<td>2.7†</td>
<td>—</td>
</tr>
<tr>
<td>TMA-4</td>
<td>2,3,5</td>
<td>1 0 1.0</td>
<td>&lt;7†</td>
<td>0.9</td>
</tr>
<tr>
<td>TMA-3</td>
<td>2,3,4</td>
<td>0.6 0 0.6</td>
<td>&lt;2†</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Expressed as the ratio of the effective dose of mescaline (3.75 mg/kg as the base) to the effective dose of a given drug.
† Expressed as ED₅₀ of mescaline/ED₅₀ of compound evaluated.¹⁸
‡ Shulgin, A. T., personal communication. TMA-5 and TMA-4 were not tested at doses high enough to determine exact potency.

the possibility of intramolecular hydrogen bonding as a stabilizing factor, and the structure-activity relationships predicted by this model.

Tryptamine Derivatives.—There are marked differences in psychedelic potency among the N-alkylated tryptamines. N,N-dimethyltryptamine (DMT) is an active psychedelic drug, effective in humans at a dose of 1 mg/kg intramuscularly, hence with a potency of about 4 mescaline units (MU, as defined in Table 1).⁶

Psilocin, or 4-hydroxy-N,N-dimethyltryptamine (Fig. 2), is a strong psychedelic compound, active at 0.12 mg/kg, with a potency of about 31 MU.⁷ Bufotenine, or 5-hydroxy-N,N-dimethyltryptamine, which differs from psilocin only in the position of the hydroxyl grouping, is not an active psychedelic compound in any dosage tested.⁸

All of these compounds possess the indole moiety of LSD (rings A and B). The side chain of these compounds can fold back on the indole ring to approximate the C ring of LSD. However, since the side chain is freely rotating, it can assume a great number of other conformations. In order to retain the C ring, there must be a means of stabilizing this particular conformation. In the molecular model of psilocin (Fig. 2), the amine moiety of the side chain approaches the hydroxyl group of the benzene ring and physically permits hydrogen bonding between the two groups. Such hydrogen bonding with the hydrogen of the 4-hydroxyl and the tertiary amine nitrogen would stabilize a
7-membered ring that, in three dimensions, closely resembles ring C of LSD. The distance between the groups forming the bond would be 1.7 Å, which is in the range of values seen for strong hydrogen bonds. The atoms illustrated for psilocin, mescaline, and 2,4,5-trimethoxyamphetamine (TMA-2) (Figs. 2, 3, and 5) are brought closer together than 1.7 Å. Intramolecular hydrogen bonding of this type cannot take place for bufotenine or DMT. Thus the structure of psilocin, the most potent psychedelic tryptamine derivative, favors the approximation of the LSD configuration more so than do the structures of the less potent tryptamines.

Phenylethylamines.—The only phenylethylamine known to be an active psychedelic agent is mescaline (3,4,5-trimethoxyphenylethylamine) (Fig. 3), and the only structural feature common to both mescaline and LSD is the benzene ring. It would be possible, however, for the amine side chain of mescaline to fold back either to position 2 or 6 ortho (adjacent) to the side chain and approximate an indole ring equivalent to ring B of LSD (Fig. 3). This conformation might be stabilized, and hence occur more frequently in vivo, by hydrogen-bonding between the hydrogen of the amine side chain and pi electrons of the benzene ring at C-2 or C-6. The extent of this intramolecular hydrogen-bonding would depend on the magnitude of the electronegative charge of the pi electrons at C-2 and C-6. Of all six isomeric trimethoxyphenylethylamines, the negative pi charge at positions 2 and 6 is greatest in mescaline, indicating that ring B could be formed more readily in mescaline than in the other isomers. Few of the trimethoxyphenylethyl amines have been tested for psychedelic action in man. 2,3,4-Trimethoxyphenylethylamine, which would not readily form ring B, is inactive in man.

Intramolecular hydrogen-bonding with pi electrons of a benzene moiety as postulated here has been described by Trifan et al. for alpha-hydroxyethylferrocene.

Amphetamines.—A great number of trimethoxyamphetamine and methoxy-methylenedioxyamphetamine have been synthesized and evaluated for psychotropic effects in man. The relative activities of several of these compounds have been confirmed in animal behavioral tests. There are marked differences in potencies between the six isomers of trimethoxyamphetamine (Table 1 and Fig. 4). Thus 3,4,5-trimethoxyamphetamine (TMA), the amphetamine analogue of mescaline, is about twice as active as mescaline, while 2,4,5-trimethoxyamphetamine (TMA-2) is 18 times as active and 2,3,4-trimethoxy-
ampheta mine (TMA-3) is inactive. Since both active and inactive TMA derivatives are metabolized at similar rates (Mitoma, personal communication), the marked discrepancies in potencies cannot be explained by differences in the rate of metabolic degradation.

Just as with the phenylethylamines, the side chain of the amphetamine derivatives can hydrogen-bond with the pi electrons at positions 2 and 6 to form ring B of LSD. In addition, in isomers with methoxy substituents at C-2 or C-6, hydrogen-bonding could take place between the hydrogen of the amine side chain and the oxygen of a methoxy group at C-2 or C-6 to form a 7-membered ring that, sterically, closely resembles ring C of LSD (Fig. 5). Thus, it would be possible for certain of the trimethoxyamphetamines to form both rings B and C of LSD, although no one molecule could assume more than a two-ring conformation at any given time.
As mentioned in discussing the phenylethylamines, the major consideration in the tendency of amphetamine molecules to form ring B would be the negative pi charge at positions 2 and 6. Such bonding could not occur in TMA-5 and TMA-6, as each of these structures contain methoxy substituents at both C-2 and C-6. Among the compounds that lack substituents at either C-2 or C-6, TMA and TMA-2 have relatively high negative pi charges at these positions (−0.1040 at both C-2 and C-6 for TMA, and −0.0721 at C-6 for TMA-2). TMA-4 and TMA-3, on the other hand, have considerably less negative pi charge at the unsubstituted C-6, −0.0527 for TMA-4 and −0.0582 for TMA-3. Accordingly, the tendency of the trimethoxyamphetamines to form ring B would be greater in TMA and TMA-2 than in TMA-4 and TMA-3.

Although it is not clear whether the tendency to form ring B by intramolecular hydrogen-bonding is related linearly to negative pi charge, it is likely that pi charge is an important consideration. As an approximation, the tendency of TMA to form ring B has been assigned a value of 1, and the tendencies of the other trimethoxyamphetamines have received valuations proportional to their relative negative pi charge at C-2 or C-6 (Table 1).

In the formation of ring C by methoxylated amphetamines, the methoxy group at C-3 must fulfill a relatively rigid spatial arrangement. Molecular models show that if there is a methoxy group at C-3, ortho to the methoxy group at C-2, the free rotation of the methoxy at C-3 would sterically hinder the ability of the C-2 methoxy to assume its required arrangement. This steric hindrance should hamper the formation of ring C in TMA-4 and TMA-3 and in 2,3,4-trimethoxyphenylethylamine. This phenomenon would interfere with ring C formation for the methoxy group at C-2 of TMA-5, but ring C could still form with the methoxy at C-6. TMA-2, on the other hand, could readily form ring C with its methoxy group at C-2, and TMA-6 could form ring C with methoxy groupings at either C-2 or C-6.

Although the stability of hydrogen-bonding for the trimethoxyamphetamines is probably greater in the formation of ring C than ring B, it is difficult to ascertain the extent of this difference. We estimated that the stability of the bond forming ring C would be twice that of the hydrogen bond in the formation of ring B by TMA. Thus, as an approximation, the tendency for formation of ring C where not prevented by steric hindrance of an orthomethoxy has been assigned a valuation of 2. The calculation for TMA-2 would be as follows:
The tendency to form ring C by bonding between the methoxy at C-2 and the amine side chain has a valuation of 2 units. Possible bonding of the amine side chain to the pi electrons at C-6 is 0.7 units, since the negative pi charge at C-6 in TMA-2 (0.0721) is 70 per cent of this value for TMA (0.1). The total tendency to approximate an LSD configuration is 2.7 units.

The ring-forming abilities of the six trimethoxyamphetamines and the potency of these compounds in both humans and monkeys are closely correlated (Table 1). Relative potencies of the trimethoxyamphetamines in rats tested in an underwater swimming task\(^7\) or a shuttle-box avoidance procedure\(^9\) were similar to the potencies shown in monkey and man.

**Methoxymethylenedioxyamphetamine.**—These compounds are analogues of the trimethoxyamphetamines in which methylenedioxy groups replace two adjacent methoxys (Fig. 4). The isomers that are comparable to TMA, TMA-2, and TMA-3 have been synthesized and tested in human subjects.\(^14\) 3-Methoxy-4,5-methylenedioxyamphetamine (MMDA), the analogue of TMA, has a potency of 2.7 MU, similar to TMA. 2-Methoxy-4,5-methylenedioxyamphetamine (MMDA-2), the analogue of TMA-2, has a potency of 21 MU, similar to TMA-2. 2-methoxy-3,4-methylenedioxyamphetamine (MMDA-3a) is the analogue of TMA-3. With a potency definitely less than 2 MU, TMA-3 is inactive as a psychedelic agent. Surprisingly, MMDA-3a, the analogue of TMA-3, is a very active psychedelic compound (18 MU), comparable in potency to TMA-2. The striking difference in activity between TMA-3 and MMDA-3a can be explained by their relative capacities to form ring C of LSD by intramolecular hydrogen-bonding. As mentioned above, ring C cannot be formed in TMA-3 because of steric hindrance by the freely rotating methoxy at C-3. In MMDA-3a, the methylenedioxy substituent constitutes a rigidly fixed linkage between C-3 and C-4 so that there is no steric hindrance to the formation of ring C by the methoxy at C-2. The ring-forming tendencies in the methoxymethylene-dioxyamphetamines thus correlate well with the potency of these compounds (Table 1). The negative pi charges of the methoxymethylenedioxyamphetamines have not been calculated but have been assigned values, the same as those of the corresponding trimethoxyamphetamines.

**Dimethoxymethylenedioxyamphetamine.**—Only two of these compounds have been synthesized and tested in humans. 2,5-Dimethoxy-3,4-methylenedioxyamphetamine (DMMDA) (Fig. 4) is equivalent to MMDA-3a with an additional methoxy grouping at C-5. As with MMDA-3a, both rings B and C can be readily formed. DMMDA is an active psychedelic agent, since it has a potency of 12 MU.\(^16\)

2,3-Dimethoxy-4,5-methylenedioxyamphetamine (DMMDA-2) differs from DMMDA only in the position of the methylenedioxy bridge. However, it is less than half as potent (5 MU) as DMMDA.\(^16\) The decreased potency is readily explicable in terms of the relative capacity of the methoxy at C-2 to form ring C with the side-chain amine. In DMMDA-2, just as in TMA-3, there is a freely rotating methoxy grouping at C-3 that would sterically hinder any hydrogen-bonding between the methoxy at C-2 and the side chain.

Recently, 2,5-dimethoxy-4-methylamphetamine (DOM) has been used illic-
ently and informally designated "STP." This compound is analogous to TMA-2, in which the methoxy grouping at C-4 has been replaced by a methyl substituent, but is five times as potent as TMA-2. Its enhanced potency may be related to slower metabolic degradation, since DOM would be resistant to demethylation at C-4, a major metabolic pathway for paramethoxylated phenylethylamines.

Most of the amphetamine derivatives described above have three methoxy substituents. The steric model described here does not require a trimethoxy compound for hallucinogenic activity. Greater importance is attached to the presence of an orthomethoxy grouping that can hydrogen-bond with the side chain. Shulgin (personal communication) has synthesized 2,5-dimethoxyamphetamine (2,5-DMA) (Fig. 4) and observed its potency in man as between 8 and 10 MU. This compound corresponds to TMA-2 with the absence of the methoxy at C-4. 2,5-DMA is considerably more potent than TMA, TMA-3, or TMA-4, all of which have three methoxy groupings. The methoxy at C-2 of 2,5-DMA can hydrogen-bond freely with the side-chain amine. Hydrogen-bonding of the side-chain amine with the pi electrons at C-6 can take place, but, since the negative pi charge at this position is considerably less than in TMA-2, this interaction would be weaker than with TMA-2. Thus the steric model would predict that 2,5-dimethoxyamphetamine should be less potent than TMA-2 or TMA-6 but more potent than TMA, TMA-3, and TMA-4. This prediction corresponds to the observed potency of 2,5-dimethoxyamphetamine in humans.

3,4-Methylenedioxyamphetamine (MDA) (Fig. 4) is another disubstituted amphetamine with psychedelic activity, whose potency is similar to 3,4,5-trimethoxyamphetamine (TMA). Although no molecular orbital calculations have been made for this compound, it is probable that the negative pi charge at C-2 and C-6 would be similar to or slightly less than the corresponding values for TMA. Thus the tendency of MDA to form ring B of LSD by intramolecular hydrogen-bonding between the side-chain amine and pi electrons at C-2 and C-6 would resemble such tendencies in TMA, and might account for the similar potency of these compounds.

The steric model described here can predict the activity of a number of psychedelic drugs. We have suggested that a tendency for intramolecular hydrogen-bonding could produce the proposed configurations. Daly has independently suggested that in vivo psilocin might achieve a configuration resembling the C ring of LSD.

In a previous study, we described a correlation between the potency of psychedelic drugs and the energy of their highest occupied molecular orbital. This correlation with electronic energy was valid only for compounds which first fulfilled whatever steric considerations are required for psychedelic activity.

If a compound satisfies the steric requirements for psychedelic activity, its potency might then be related to electronic considerations. Thus, both 2,4,5-trimethoxyamphetamine (TMA-2) and 2,4,6-trimethoxyamphetamine (TMA-6) fulfill the steric requirements described here. Since the side-chain
amine presumably can hydrogen-bond more strongly to an orthomethoxy group-
ing than to pi electrons, the steric model would suggest that TMA-6 might be
more potent than TMA-2. Molecular orbital calculations indicate a less
energetic highest occupied molecular orbital for TMA-6 than for TMA-2
(Merril, unpublished observations). In tests of both monkeys* and humans
(Shulgin, personal communication), TMA-6 is a highly active psychedelic agent,
but somewhat less potent than TMA-2. These results would suggest that since
both of these compounds have fulfilled the steric requirements for psychedelic
activity, their potency is then related to the energy of the highest occupied
molecular orbital.

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