the effect of LSD was inhibited. This dose of THPC by itself produced no behavioural effect (Figs. 2 and 3).

THPC could potentiate the effect of mescaline by one of two mechanisms: (i) if mescaline occupies only half the LSD site, as Snyder and Richelson have proposed[6], occupation of the other half by THPC might increase its effect, at the same time blocking binding of LSD, or (ii) THPC might affect some other brain mechanism, which, although it might have no direct behavioural effect, would nevertheless potentiate the effect of mescaline on some other system. But because mescaline and LSD are believed to act on the same mechanism, it is difficult to see why such a non-specific action should not potentiate the effect of LSD as well.

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Correlation between Activity and Electronic State of Hallucinogenic Amphetamines

THE actions of hallucinogenic agents have been correlated with Hückel molecular orbital calculations of the π-electrons[1] and with fluorescent properties[2]. The Hückel correlations on three methoxylated amphetamines indicated that hallucinogenic activity correlated with energy of the highest occupied molecular orbital[1].

We calculated the total valence electron charge density, frontier electron density, dipole moment, total energy and all energy levels of thirteen hallucinogenic amphetamines using the INDO method (intermediate neglect of differential overlap)[3] which gives good results in the calculation of dipole moments, molecular geometries, electron nuclear hyperfine coupling constants and force constants[4–7]. Standard bond lengths and bond angles were used to generate cartesian coordinates, and vicinal methoxy groups were regarded as out of plane in a *trans*-configuration. All results were subjected to sequential multiple regression analysis.

Table 1 shows the correlation between hallucinogenic activities in man[8] and the energy of the highest occupied molecular orbital (E_H). For this correlation, the linear regression equation, log $A = a + bx_1 + cx_2$ . . ., may be expressed by the following equation, where A is hallucinogenic activity

$$\log A = 19{\cdot}07 + 35{\cdot}65\ E_H \qquad (1)$$

The equation for equimolar activity is

$$\log A = 18{\cdot}7 + 35{\cdot}1\ E_H \qquad (2)$$

For equation (1), $r = 0{\cdot}753$, $F = 14{\cdot}36$ and $P < 0{\cdot}005$; for equation (2), $r = 0{\cdot}756$, $F = 14{\cdot}62$ and $P < 0{\cdot}005$. This correlation suggests that the ease of perturbability of the π-electrons of the amphetamines is a determinant of hallucinogenic activity, the amphetamines presumably forming with the brain receptor a low energy, reversible π-molecular complex that gives rise to hallucinations.

Table 1. HALLUCINOGENIC ACTIVITIES OF AMPHETAMINE DERIVATIVES IN MAN AND ENERGY OF THE HIGHEST OCCUPIED MOLECULAR ORBITAL (E_H)

Derivative of amphetamine	Hallucinogenic activity	E_H (atomic units)
2,5-$(OCH_3)_2$-4-CH_3	80–100*	−0·4929
2,4,5-$(OCH_3)_3$	17	−0·5001
2,3,6-$(OCH_3)_3$	13	−0·5112
2,4,6-$(OCH_3)_3$	10	−0·5217
2,5-$(OCH_3)_2$	8	−0·5012
2,3,4,5-$(OCH_3)_4$	6	−0·5126
2,4-$(OCH_3)_2$	5	−0·5194
4-OCH_3	5	−0·5262
2,3,5-$(OCH_3)_3$†	4	−0·5026
3,4,5-$(OCH_3)_3$	2	−0·5218
2,3,4-$(OCH_3)_3$	< 2	−0·5274
3,4-$(OCH_3)_2$	< 1	−0·5238
(Mescaline)‡	1	−0·5226
(Amphetamine)	0	−0·5885

* The activity has been reported as 80 and 100[2,8].
† Limited number of tests.
‡ Mescaline, 3,4,5-trimethoxyphenylethylamine, is not an amphetamine derivative but is used as a standard of hallucinogenic activity[8]. Amphetamine is not hallucinogenic and is not considered in the statistical analysis.

Table 2. E_H OF SOME UNTESTED AMPHETAMINE DERIVATIVES AND THEIR PREDICTED HALLUCINOGENIC ACTIVITIES

Derivative of amphetamine	E_H (atomic units)	Predicted activity
2,3,4,6-$(OCH_3)_4$	−0·5067	10·0
3,5-$(OCH_3)_2$	−0·5240	2·4
4-OH	−0·5296	1·5
3-OCH_3	−0·5316	1·3
2,6-$(OCH_3)_2$	−0·5334	1·1
2,3-$(OCH_3)_2$	−0·5346	1·0
2-OCH_3	−0·5371	0·9

Equation (1) was used for the predictions; equation (2) gives very similar results.

Although the correlation is significant ($r = 0{\cdot}753$, $F = 14{\cdot}36$, $P < 0{\cdot}005$), E_H does not account for the activities of all the compounds. The 2,3,6-trimethoxy and 2,4,6-trimethoxy derivatives and the 4-methoxy derivative are more active than expected if E_H is the only determinant of activity; and the 2,3,5-trimethoxy is less active. Other electronic or steric characteristics not revealed by this work could contribute to the activity. A better correlation cannot be expected. Drugs are involved in numerous interactions[9] before they induce hallucinations. Also, the error in measuring relative hallucinogenic activity in man is about 20 per cent (personal communication from A. T. Shulgin). Assuming that E_H is the only correlate of activity, we calculated the expected hallucinogenic activity of some untested amphetamines (Table 2). Of these, the 2,3,4,6-tetramethoxy derivative is the only one that should be significantly more potent than amphetamine. Shulgin states in a personal communication that the 2,3,4-trimethoxy derivative has measureable activity, but it is less than two[8]; our calculations predict that it has about the same activity as mescaline.

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