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Structure-activity Studies on Hallucinogenic Amphetamines using Model Interaction Calculations

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In summary, we can briefly describe the model as developed at this time. We view the amphetamine receptor as possessing two principal features: one site provides anchoring for the onium group, whereas the other feature interacts with the phenyl ring and substitutents. In addition, there is implied the presence of a feature associated with the 3,4 region of the phenyl ring. The best model for the phenyl ring receptor is the methylindole molecule with the two rings, one directly above the other at a separation distance of 4·5 Å. The correlation from these results [equation (2)] is better than that reported for any other SAR study to date, accounting for 74% of the variation in the data. Further inclusion of a term relating to distribution or absorption improves the correlation so that 82% of the variation is accounted for.

This provisional model can now be tested against data for other amphetamines, mescalines, tryptamines and other hallucinogenic agents.

1. Introduction

The past decade has produced some interest in the study of structural features of molecules imparting hallucinogenic activity. Because of the greater abundance of biological potency data among amphetamine derivatives, this class of molecules has been the principal target of study (Shulgin, Sargent & Naranjo, 1969; Shulgin & Dyer, 1975).

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The first of these studies (Snyder & Merril, 1965), was a calculation of the pi-electron Huckel energy of the highest occupied molecular orbital, *E(HOMO)* of the substituted aromatic rings. This energy was compared to the potency of ring-substituted amphetamines, expressed as ratios of effective doses to a mescaline (3,4,5-trimethoxyphenethylamine) standard. They found a relationship, interpeted as signifying a possible complex between the aromatic ring and a receptor feature. The complex was thought to be a charge-transfer event in which the ring was a net donor of electrons.

Chothia and Pauling discussed existing data on the substituted amphetamine class and drew certain conclusions about the probable conformations of methoxyl groups found within this class (Chothia & Pauling, 1969). Kang & Green calculated the *E(HOMO)* within the amphetamine class using an all-electron molecular orbital method (Kang & Green, 1970). They also found that this energy exhibited some relationship to the mescaline-relative potency. Although the regression analysis of this relationship explained only one-half of the variation in the activity, their work reinforced the conclusions of Snyder & Merril that the ring was likely involved at some receptor feature in an interaction quantifying the response.

In a study attempting to relate potency with a physical property, Barfknecht examined the octanol–water partition coefficients of a series of substituted amphetamines (Barfknecht, Nichols & Dunn, 1975). It is hard to make a firm structural interpretation of these results in view of the modest correlation found and the uncertainty about the structural interpretation of the partition coefficient. Nevertheless, the results are compatible with previous conclusions about the important role of the aromatic ring in the amphetamine hallucinogenic class.

Sung & Parker (1972) have measured association constants by NMR between several substituted amphetamines and 1,4-dinitrobenzene. They found a correlation between the association constant and potency, after deleting three molecules from the twelve studied.

This accumulated evidence suggests that hallucinogenic potency among the amphetamine derivatives likely depends on the common onium group and to a quantitative degree, the ability of the ring to engage in an optimum interaction with a second receptor feature. In our studies on the structure–activity relationship in this class of hallucinogenic agents, we have adopted as operational hypotheses the accumulated conclusions just described.

There are certain advances beyond these studies which, we feel, might lead to a more significant correlation between activity and structure. In the first case, the structural descriptions considered to date have all been on static molecules, isolated from each other or from the receptor. In our view, an effort should be made to create a dynamic model of interacting species,

and to attempt to predict energies of such interactions. Secondly, there is a limit to the amount of information to be gained from the consideration of a single molecular orbital theory index such as *E(HOMO)* as characterizing a complicated interaction process. That these high-lying orbitals are important cannot be denied, but we feel that they are just part of the overall picture in quantitating the interaction of two molecular species. These considerations have led us to approach the study of amphetamine hallucinogenic SAR from an interacting point of view.

2. Model Interaction Energy Calculations

We have recently utilized an approach to quantitative structure–activity studies of drug molecules, which we call *receptor mapping using model interaction energy calculations* (Kier & Aldrich, 1974; Holtje & Kier, 1974, 1975). The method consists of the calculation of the interaction energy between a part of a drug molecule under study, and a model compound, chosen to simulate a likely receptor feature. In this case we focus attention on the amphetamine aromatic ring and substituents. A series of interaction energy calculations are made using the same receptor model but varying the drug molecule feature. By comparing the calculated interaction energies in this series, at some constant orientation and distance from the receptor model, we hope to find a correlation between the energies and the biological activities. If the receptor model is well-chosen, such a correlation may be found and we can then claim that our model system is behaving in a manner isomorphic with reality. The value of a good isomorphic model lies in its ability to predict activity or to create rationale for further compound design.

The creation of the dynamic model begins with the assumption utilized by Burgen (1965) as well as Villa & Grana (1967) that variation in drug potency may be related to variation in interaction energy within a related series of molecules. The equation to express this relationship is $\Delta E = -RT \ln P$, where P is the ratio of biological activities. The relationship may be utilized in studies on a series of molecules in which one structural feature is varied. As in our previous papers, we relate calculated interaction energy to biological response which is, in turn, related to the logarithm of the concentration necessary to elicit a standard response. This latter is the traditional log dose–response relationship.

In the amphetamine case, as shown in Fig. 1, one part of the molecule, the onium group, may bind in an identical fashion to the appropriate receptor feature. Because of the anchoring at feature A in each molecule, the approach of the aromatic ring to receptor feature X is considered to be identical through a series of congeners. The problem then reduces to the proper choice of

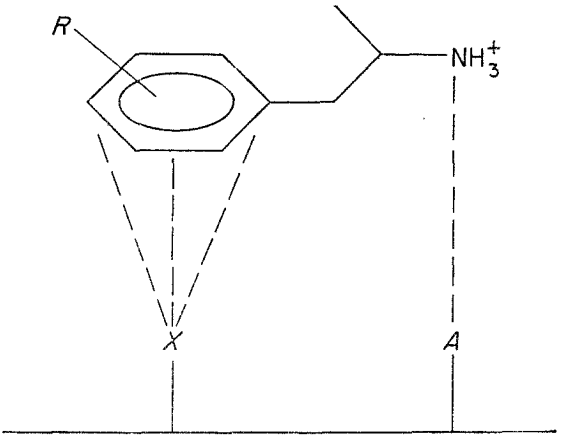

FIG. 1. Model of amphetamine congener and hypothetical receptor interaction.

receptor model, X, and the intervening distance, d, which will give interaction energies correlating with the activities. The value of any such correlation takes on significance with a large number of molecules in the series.

The orientation of the drug molecule feature to the receptor feature is a variable to be considered. Since anchoring of the molecule through the onium group is presumed to occur, the freedom in the alignment of the ring to a receptor feature is limited. We confine our search pattern to modest separation and translation dimensions but consider all possible in-plane rotation angles of the amphetamine ring.

For the calculation of the interaction energies, we have employed the monopole-bond polarizabilities method developed by Claverie & Rein (1969). The interaction energy is a sum of the electrostatic, polarization, dispersion and repulsion energies, between all atoms of the two model compounds. The method employs the charge densities at each atom, predicted from molecular orbital calculations. We also employ the experimental parameters of polarizability and ionization potential. The actual working equations are given in the Appendix.

These calculations have been used by Rein to predict interaction energies between DNA bases and amino acids (Rein, Rendell & Harlos, 1970). Hoyland & Kier (1972) have used them in the prediction of a molecular conformation, prostaglandin E-1.

The initial use of this approach to the study of series of pharmacologically active agents was a study of acetylcholine congeners varying the onium group (Kier & Aldrich, 1974). A good correlation was found between the interaction energy and hydrolysis rate of enzyme substrates ($r = 0{\cdot}97$) in another

study (Holtje & Kier, 1974). Sweet-tasting nitroaniline analogues were found to exhibit interaction energies with a receptor model, correlating with a sweet taste potency ($r = 0{\cdot}89$) (Holtje & Kier, 1974). A series of chloroamphenicol congeners was also tested by this method to yield an energy–potency relationship ($r = 0{\cdot}91$) (Holtje & Kier, 1974). Cholinesterase inhibitors were also examined to study the nature of the anionic site (Holtje & Kier, 1975). Holtje has used this approach in a productive study of a series of monoamineoxidase inhibitors (Holtje, 1975).

3. Development of Amphetamine–Receptor Interaction Model

(A) CHOICE OF RECEPTOR MODEL

The choice of a reasonable receptor model, described by X in Fig. 1, is a critical part of the study. We began with the common assumption that receptors are most likely composed of molecular fragments of proteins, in particular, the amino acid residue side chains. This has been the choice in previous studies (Kier & Aldrich, 1974; Holtje & Kier, 1974, 1975; Holtje, 1975). Our studies further revealed that the aromatic side chains of amino acids were superior in generating interaction energies of sufficient range and ranking to correlate with potency. In particular, we found that toluene, surrogate for the phenylalanine side chains and methylindole, surrogate for the tryptophan side chain were the best models in our studies to date.

It must be emphasized here, as we have done in the past, that these previous results, or our anticipated results with amphetamines, do not establish phenylalanine or tryptophan side chains as receptor features. It only establishes these moieties as good models, simulating reality in our model system.

In our present studies we have tested the aromatic molecules, simulating the aromatic side chains of amino acid residues. The best model in preliminary studies was found to be methylindole. This model, in a large number of interaction calculations with substituted benzene rings of the hallucinogenic amphetamines, results in the best relationship of energy to potency.

This model is superior for two possible reasons. The indole ring presents a large enough surface area so that coplanar approaches of amphetamine rings to indole will bring about effective interactions with many of the substituent groups found in the series. Thus the resulting interactions, which are responses to these groups, give rise to different potencies. The model is also superior, say to benzene, because of the unsymmetrical charge pattern around the indole ring system. In contrast, benzene is too symmetric in this sense, to afford a unique discrimination of interactions with the substitution pattern of the amphetamines. Imidazole, surrogate for the side chain of histidine,

meets this second criterion, but fails in the first one, being too small in area to embrace many of the amphetamine ring substituents in a significant manner.

(B) SIDE CHAIN CONFORMATION

The isopropyl ammonium side chain of the protonated amphetamines has been studied in several laboratories for its conformational preference. X-ray analysis reports a preference for the conformation in which the amino group is gauche to the ring (Baker, Chothia & Pauling, 1973); semi-empirical molecular orbital calculations predict an equal preference for the amino group or the methyl group to be gauche (Pullman, Coubeils, Courriere & Gervois, 1972; Kang, Johnson & Green, 1973); *ab initio* M.O. calculations report a prediction of the amino group gauche (Hall, Miller & Schnuelle, 1975); empirical potential function calculations predict the methyl group to be gauche (Weintraub & Hopfinger, 1973); NMR analysis results in an interpretation favoring a gauche methyl group (Bailey, By, Graham & Verner, 1971); comparative studies with another rigid hallucinogenic agent, LSD, lead to a postulation of the methyl group oriented in a gauche conformation (Chothia & Pauling, 1969; Kang & Green, 1970). We have adopted the conformation in which the amino group is trans to the ring in these studies on the basis of the NMR analysis (Weintraub & Hopfinger, 1973), the comparative models of Chothia (Chothia & Pauling, 1969) and Green (Kang & Green, 1970), and our own calculations using CNDO/2. The *R* configuration was considered in this study, based on the finding of Shulgin (1973) of some stereospecificity among the hallucinogenic amphetamines.

(C) METHOXYL GROUP CONFORMATIONS

It is evident that the presence and pattern of substitutents on the ring of hallucinogenic amphetamines plays a key role in the quantitative response of these molecules. This has been enunciated by Shulgin, Sargent & Naranjo (1969), Baker, Chothia & Pauling (1973), Kang & Green (1970), and Barfknecht, Nichols & Dunn (1975). It is essential, then, that the assignment of the conformation of the methoxyl groups reflects reality as closely as possible, since the interaction energy we calculate is dependent on the orientation of these substituents.

The evidence from theory and experiment is conflicting and inconclusive. X-ray studies on condensed phases tend to indicate in-plane methoxyl conformations whereas isolated molecule calculations (Kang & Green, 1970; Baker, Chothia & Pauling, 1973; Kang, Johnson & Green, 1973; Weintraub & Hopfinger, 1973) tend to indicate non-coplanar arrangements.

Our own calculations lead us to the following assignments of methoxyl group conformation (see Fig. 3):

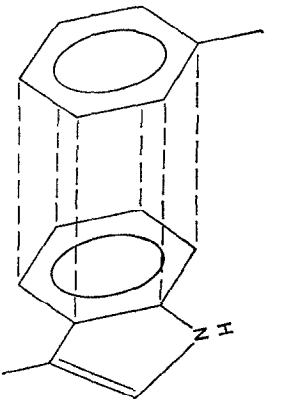

FIG. 2. Optimum mode of interaction predicted for amphetamine rings and the methylindole receptor model.

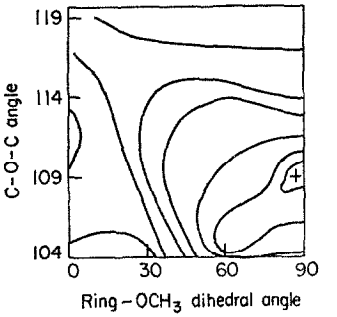

FIG. 3. Isoenergy contours for methoxybenzene. Intervals are 0·001 a.u. The x-axis is the dihedral angle of the O—CH_3 bond with the benzene ring: 0° is in plane, 90° perpendicular. The Y-axis is the bond angle ring-O-CH_3. The energy minimum is marked with a "+".

(a) Isolated methoxyl groups in positions 3–5 are above or below the ring phase, (b) adjacent methoxyls are antiparallel out of plane, (c) methoxyl groups in the 2 and 6 positions are below the ring plane relative to the side chain. All combinations of methoxyl group conformations consistent with the above assignments are considered in the interaction calculations and the mean of the energies is used for each congener.

This averaging procedure is based upon our earlier stated assumption that the interaction energy is directly proportional to the biological response.

The methylenedioxy-groups are nearly in the ring plane. We presume that the puckering of this 5-membered ring can reverse itself easily; hence, we have chosen a planar arrangement as an average approximation.

The interaction energies were nearly identical for the puckered and planar conformations in several preliminary runs, justifying this simplifying assumption.

(D) RING CHARGE CALCULATIONS

The electronic charges have been calculated for each amphetamine derivative using the CNDO/2 method, for subsequent use in interaction calculations. Each ring position or substituent atom was found to exhibit a fairly constant value in spite of the changes which may occur two atoms removed. The major influence, of course, occurs with changes of atoms directly bonded.

An indication of the relative importance of the electrostatic interaction [E_e in equation (A1), Appendix] can be seen from the following typical results. For each molecule listed the following component energies are given: electrostatic, polarization, dispersion, repulsion, total, respectively in kcal.

For 2-methoxy-3,4-methylenedioxy-amphetamine: $-0{\cdot}552$, $-0{\cdot}560$, $-5{\cdot}380$, $+1{\cdot}015$, $-5{\cdot}514$; 2,5-dimethoxy-4-ethoxyamphetamine: $-0{\cdot}441$, $-0{\cdot}493$, $-5{\cdot}468$, $+0{\cdot}590$, $-5{\cdot}812$; 3,4-dimethoxy-amphetamine: $-0{\cdot}700$, $-0{\cdot}545$, $-4{\cdot}700$, $+5{\cdot}89$, $-5{\cdot}356$.

Examination of these energy results show that the electrostatic term accounts for about 10% of the total interaction energy for the typical case. Hence, electrostatic interaction does not play a dominant role in the interaction. It is expected that the charges attributed to the atoms will, then, not be significantly perturbed over the range of interaction distances chosen for this study. On this basis we have proceeded to use CNDO/2 calculated charges based upon isolated molecules.

(E) CONSIDERATION OF ACTIVITY DATA

The data generated by Shulgin, Sargent & Naranjo (1969) is an interpolated estimate of the dose necessary to produce a 50% response. This is compared to the comparable effective dose for mescaline and expressed as a ratio, termed the mescaline unit. We have converted the mescaline units to molar mescaline units by expressing the doses in molar quantities.

The estimate of Shulgin is that the accuracy of the data may be only 25%. As a consequence, correlations with this data that exhibit correlation coefficients above 0·90 may lose relevance in view of the large variation in the expected accuracy of the data.

Finally, for our work, we have employed the log of the mescaline unit potency. These values are listed in Table 1. We have chosen these seventeen substituted amphetamines for the initial phase of our work on the basis of their possession of alkoxy ring substituents, methoxyl, ethoxyl and methylenedioxy groups.

A problem arises when data is expressed as "less than" a certain mescaline unit. This occurs in five cases among the amphetamine derivatives reported. We deleted these molecules from consideration in order to achieve the most reliable correlation.

(F) RING CONFORMATION CONSIDERATION

The symmetry of the phenyl ring in unsubstituted amphetamine would permit the two ring conformers 180° apart, relative to the side chain, to coexist with equal energy. Likewise, symmetrically substituted amphetamines would constitute a similar case. Our comparison of the preferences of the 3,4-disubstituted amphetamines with the 180° rotamers, reveals an energy difference of less than 0·1 kcal, using CNDO/2 M.O. calculations. It can be assumed, therefore that both rotamers would nearly equally coexist. In the case of unsymmetrical 2-position substituted amphetamines, the preference for the isomeric 6 position of the ortho substituent amounts to about 0·2 kcal, based on our CNDO/2 M.O. calculations. Again, we can assume that this difference is modest enough so that both rotamers, differing by 180°, must be considered as contributors to the total population of molecules. To illustrate this point, the 3,4-dimethoxy analogue will coexist with the 4,5-dimethoxy isomer in free space. As these two approach the receptor, they will reach a separation distance from the receptor which will prohibit the inter-rotation between the two isomers. The half-widths of the 3,4-dimethoxy (or 4,5) is such that the barrier to rotation is insurmountable within a separation distance of about 6 Å. The isomers are thus committed to their conformations as they close the distance to the receptor. The measured response is therefore an average of these two interaction effects on the receptor.

The consequence of this evaluation is important to our study of the interaction energies between hallucinogenic amphetamines and model compounds, surrogate for receptor features. Thus, if the 2,4,5-trimethoxy amphetamine can exist in both 180° conformers of the ring, then the complementary ring substituted pattern, which we call the 3,4,6-trimethoxy amphetamine must also be studied for its interaction energy with the receptor model. This complicates our study to the extent of requiring us to examine almost twice the number of interactions for a list of substituted amphetamines. The complementary ring isomers are listed in Table 1.

TABLE 1

Substituted amphetamines with experimental and predicted activities

Ring substitution	Ring isomer	obs. log MU	calc. log MU	Interaction *E*
4-MeO	—	0·59	0·64	4·58
2,4-MeO	4,6-MeO	0·67	0·97	5·77
2,5-MeO	3,6-MeO	0·87	0·82	5·21
3,4,5-MeO	—	0·37	0·41	4·72
2,3,5-MeO	3,5,6-MeO	0·63	0·81	5·20
2,4,6-MeO	—	1·03	1·30	6·97
2,3,6-MeO	2,5,6-MeO	1·14	1·14	6·39
2,4,5-MeO	3,4,6-MeO	1·26	0·95	5·68
2,3,4,5-MeO	3,4,5,6-MeO	0·86	0·88	6·38
3,4-OMeO	4,5-OMeO	0·41	0·57	4·34
3-MeO,4,5-OMeO	5-MeO,3,4-OMeO	0·43	0·47	4·91
4-MeO,2,3-OMeO	4-MeO,5,6-OMeO	0·48	0·47	4·91
2-MeO,3,4-OMeO	6-MeO,4,5-OMeO	1·00	0·89	5·49
2-MeO,4,5-OMeO	6-MeO,3,4-OMeO	1·08	0·89	5·48
2,3-MeO,4,5-OMeO	5,6-MeO,3,4-OMeO	0·75	0·66	5·59
2,5-MeO,3,4-OMeO	3,6-MeO,4,5-OMeO	1·13	1·05	6·04
2,5-MeO,4-EtO	3,6-MeO,4-EtO	1·22	0·99	5·82

(G) INTERACTION ENERGIES CALCULATED WITH MODELS

In these studies we have calculated the interaction energies between each substituted amphetamine of the pairs shown in Table 1 and 3-methylindole, our receptor model. There are 17 amphetamines in this phase of the study, each with a reported activity. The salient question is, how much of the observed activity is due to each member of the rotational isomer pairs shown in the table? Our calculations suggest that each member of a pair is present in close to equal proportion with its complement in isolated molecule calculations. Thus each isomer must be considered to contribute to the activity. Based on our original premise that the activity is proportional to the interaction energy developed by the substituted ring, then the activity of a particular molecule is a composite value made up of activities contributed by the isomers.

We have treated this in the following way; at each separation distance and orientation between amphetamine and receptor, we have computed the interaction energies for the 17 congeners and the 14 rotational isomers, totaling 31 calculations. The 17 energies for comparison with activities were computed as a weighted average of the conformer values, each weighted by the appropriate Boltzmann factor. This weighted average value of the interaction energy was presumed to be governing the quantitative measure of the

potency for that molecule. In addition, we have computed the interaction energies for each possibility where a methoxyl group can exist either above or below the ring plane. The final energy used to relate to the potency is the weighted mean value.

The computation of energies from all isomer possibilities results in 17 energy values for each interaction mode considered. Consequently 52 energies had to be computed in each consideration of a change in orientation.

After a number of interaction energy calculations were made, it became apparent that the inter-ring separation of 4·5 to 6·0 Å was producing the best model based on subsequent correlations with activity. Further, in the opening phase of this work we considered only co-planar approaches between rings in our models.

The amphetamine rings were rotated through 360° by 30° increments for each separation distance and for each isomer. In addition, translations in the ring plane were made at 0·5 Å increments, as also were ring separation distances.

Our preliminary results indicated that a number of distances and orientations were yielding ranges of energies which would equate to the range of observed activity. The correlations, however, were not high. This led us to suspect that a particular feature of the amphetamine ring may have to be additionally considered in order to develop an adequate model. This suggests to us that a secondary receptor may be involved. As a consequence, we began a search for an additional feature whose presence would create an appropriate additional interaction.

(H) INDICATOR VARIABLE STUDY

To conclude the first phase of this study, we have begun a preliminary modeling of a secondary receptor feature which, we suspect, mitigates the main interaction energy developed by the amphetamine ring. The modeling at this stage consisted of the creation of a matrix of indicator variables to correspond with the presence of certain structural features around the ring, which may be involved in a secondary interaction. These variables identify the presence of substitutents of common type around the ring (1 for presence, 0 for absence) of groups in single and adjacent positions. Account was taken of the coexistence of 180° rotamers in 14 cases.

4. Analysis of Interaction Studies

Our calculations revealed a distinct preference, based on correlation with potency, for the amphetamine rings interacting with the methylindole receptor model as shown in Fig. 2. For each amphetamine molecule the

orientation to the methylindole molecule and the ring-to-ring distance is identical: the six-membered ring of the amphetamine is directly above the six-membered indole ring, atom above atom, at a distance of 4·5 Å. The relative orientation of the amphetamine side-chain and the indole methyl group is indicated by the line attached to the respective ring systems; they are approximately opposite to each other. The interaction energies, computed for this orientation, correlated with the log of the molar mescaline units (log A) as:

$$\log A = 0{\cdot}31E - 0{\cdot}89, \tag{1}$$

where $R = 0{\cdot}73$, $S = 0{\cdot}21$, $N = 17$, $F = 16{\cdot}7$, $P < 0{\cdot}01$. This result has statistical significance at the 99% confidence level.

Our position indicator variable study revealed that one indicator alone made an appreciable improvement in this result. That variable is the one denoting the presence of a pair of oxygen substituents in the 3,4 position with no intervening methylene group. The relationship with the potency is then:

$$\log A = 0{\cdot}28E - 0{\cdot}26I_{3,4} - 0{\cdot}63, \tag{2}$$

where $R = 0{\cdot}83$, $S = 0{\cdot}17$, $N = 17$, $F = 15{\cdot}5$, $P < 0{\cdot}001$. This equation has statistical significance at the 99·9% confidence level. The low standard deviation reveals that the equation predicts the hallucinogenic potency within 18% of the experimental value. This result should be considered in the light of the fact that the experimental value may vary by 25%.

We interpret these intermediate results to mean that a secondary receptor feature may exist so as to interact with the amphetamine ring 3,4 positions. This feature may contribute a modest additional energy of interaction. This contribution is less in those cases where the 3,4 position indicator variable is one.

Sung & Parker (1972) have correlated the activity of 12 amphetamines with the stability of molecular complexes. 1,4-dinitrobenzene was used as the acceptor. To obtain a good correlation, they excluded 3 molecules (3,4-dimethoxy amphetamine, 2,3,4-trimethoxy amphetamine, and 3,4,5-trimethoxy amphetamine) which were predicted to be more active. In the light of our results, we see that these three molecules have in common methoxys in the positions 3 and 4. This further supports our findings that there is a secondary feature located in space in the vicinity of the amphetamine ring 3,4 positions.

As a side issue, we were interested to determine whether the potency may in some way be connected with the thermodynamic properties of the molecules which govern absorption or barrier passage. We tested this by including

the partition coefficient as an additional term.

$$R = 0{\cdot}88,\ S = 0{\cdot}14,\ N = 17,\ F = 15{\cdot}00,\ P < 0{\cdot}001. \quad (3)$$

Thus, although it is not the principal factor, the absorption properties of the molecule may be a factor as suggested by Barfknecht, Nichols & Dunn (1975).

By the appropriate F test, the addition of each of the variables to the energy [equations (2) and (3)], were found to be statistically significant with a probability greater than 99·5%. The model thus created permits us to proceed with the analysis of other hallucinogenic agents. It also gives us a background to begin the search for a molecular definition of the secondary receptor feature.

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APPENDIX

The long-range interaction energy is calculated as a sum of electrostatic (E_e), polarization (E_p), dispersion (E_d) and repulsion (E_r) components:

$$E = E_e + E_p + E_d + E_r. \tag{A1}$$

For convenience the two molecules are designated by subscripts 1 and 2; N and B are the number of atoms and bonds, respectively in each molecule. The explicit formulas are as follows:

$$E_e = \sum_{i=1}^{N_1} \sum_{j=1}^{N_2} \frac{q_i q_j}{R_{ij}}, \tag{A2}$$

$$E_p = -\tfrac{1}{2} \sum_{k=1}^{B_1} \varepsilon_k \bar{\bar{A}}_k \varepsilon_k - \tfrac{1}{2} \sum_{l=1}^{B_2} \varepsilon_l \bar{\bar{A}}_l \varepsilon_l, \tag{A3}$$

$$E_d = -\tfrac{1}{4} \times \frac{I_1 I_2}{I_1 + I_2} \sum_{k=1}^{B_1} \sum_{l=1}^{B_2} R_{kl}^{-6} T_r[\bar{\bar{T}}_{kl} \bar{\bar{A}}_k \bar{\bar{T}}_{kl} \bar{\bar{A}}_l]. \tag{A4}$$

In equation (A2), q_i is the charge at nucleus i and R_{ij} is the distance between the nuclei i and j. In equation (3) ε_k is the electric field at the center of bond k (in molecule 1) due to the monopole charge qj of molecule 2,

$$\varepsilon_k = \sum_{j=1}^{N_2} q_j R_{jk} R_{jk}^{-3} \tag{A5}$$

where R_{jk} is the distance from nucleus j to the midpoint of bond k and R_{jk} is the vector of magnitude R_{jk} pointing from center j to the bond midpoint k. The quantity $\bar{\bar{A}}_k$ is the polarizability tensor for bond k.

The dispersion equation (4) contains the average excitation I_1 and I_2 approximated by the ionization potentials and a factor x which corrects for the fact that the usual London equation ($x = l$) gives a result which is too small. R_{kl} is the distance between the midpoints of bonds k and l, and the tensor $\bar{\bar{T}}_{kl}$ is defined as:

$$\bar{\bar{T}}_{kl} = 3 \frac{R_{kl} \times R_{kl} - 1}{R_{kl}^2} \tag{A6}$$

where l is the unit matrix. The symbol T_r in l-equation (A4) indicates the trace of the quantity in parenthesis.

To calculate the repulsion resulting from overlap of the charge distribution of the two molecules, the Kitaygorodski repulsion (1961) derived empirically from crystal energies of hydrocarbons and slightly modified by Huron &

Claverie (1969) has been used. This relation is:

$$E_r = 30000 \sum_{i=1}^{N_1} \sum_{j=1}^{N_2} \exp\left[-5{\cdot}5R_{ij}(V_iV_j)^{-\frac{1}{2}}\right] \qquad \text{(A7)}$$

where V_i is the van der Waals radius of atom i.

Ionization potentials and charges are from CNDO/s calculations standard bond lengths and angles were used. The polarizabilities are taken from Denbigh (1940) or le Febvre (1965). The van der Waals radii are as follows: $H = 1{\cdot}2$, C = 1·6, C (arom.) = 1·8, N = 1·5, O = 1·4, S = 1·9.