

# A crystallographic and theoretical study of the conformation of DOET and its significance for the hallucinogenic amphetamines

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The crystal and molecular structure of 2,5-dimethoxy-4-ethyl- $\alpha$ -methyl-phenylethylamine (DOET) has been determined by X-ray crystallography and the conformation of the side chain has been examined theoretically by the use of a potential energy calculation. There is no indication in the solid state of any intra or inter-molecular hydrogen bonding. The isopropylamine side chain is staggered to the plane of the benzene ring. The  $\alpha$ -methyl group is fully extended (antiplanar) whereas the amino group is orientated back towards the ring (synclinal). The potential energy calculations show the existence of 6 minima, one of which corresponds to the crystal position. The calculations also show that the energy differences between the various minima of the side chain are very small. The relationship of these data to the conformations of the hallucinogens, mescaline and 2,4,5,-trimethoxyamphetamine is discussed.

Certain methoxylated amphetamine derivatives are known to exhibit hallucinogenic activity in man (Shulgin, Sargent & Naranjo, 1969). DOM (2,5-dimethoxy-4-methyl- $\alpha$ -methyl-phenylethylamine), Fig. 1a is one of the most active compounds in this group and is reported to be 80 times more potent than mescaline Fig. 1b (Shulgin & others, 1969). Hallucinogens such as D-LSD, psilocin and the methoxylated amphetamines exhibit cross-tolerance (Brawley & Duffield, 1972) which has been taken to indicate that these molecules are acting at the same or a similar site in the CNS. This has led to various attempts to interrelate the conformations of these molecules derived from model-building (Snyder & Richelson, 1968), X-ray analysis (Chothia & Pauling, 1969; Baker, Chothia & others, 1973) and theoretical calculations (Kang & Green, 1970; Kang, Johnson & Green, 1973). To date, all the crystal structure determinations of the substituted phenylethylamine class of compounds have been carried out on salts or metal complexes (Carlstrom, Bergin & Falkenberg, 1973) where it is probable that the conformation of the side chain is strongly influenced by the geometrical requirements of the hydrogen bonding of the positively charged amino group to the counter ion. In order to obviate this restriction and to obtain an indication of the energy barriers separating the various possible conformations of the side chain, the crystal and molecular structure of the free base of DOET (2,5-dimethoxy-

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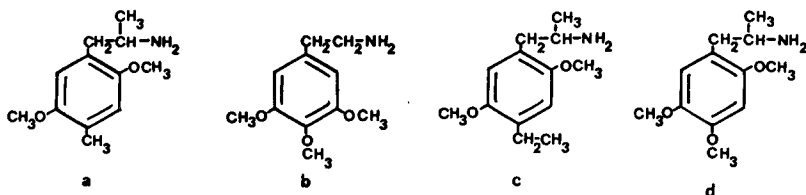


FIG. 1. a=2, 5-Dimethoxy-4-methyl- $\alpha$ -methyl-phenylethylamine (DOM), b=mescaline c=2, 5-dimethoxy-4-ethyl- $\alpha$ -methyl-phenylethylamine (DOET) d=2,4,5-trimethoxyamphetamine (2,4,5-TMA).

4-ethyl- $\alpha$ -methyl-phenylethylamine) Fig. 1c has been determined by X-ray analysis and the molecular parameters thus obtained have been used to perform a potential energy calculation on this molecule. In man in the dose range 0.7–4 mg, DOET produced mild euphoria and a feeling of enhanced self awareness and at the higher dosages a tendency to feel anxious; it is apparently more potent than DOM in terms of the minimal dose required to produce subjective psychotropic effects (Snyder, Faillace & Weingartner, 1968; Snyder, Weingartner & Faillace 1971). In animal tests DOET has a typical "hallucinogenic" profile (Aldous, Barrass & others, 1974). DOET is therefore useful as a model to test the suggestion (Snyder & Richelson, 1968) that in the free base of certain substituted amphetamines hydrogen bonding between the hydrogen atom of the primary amine and the oxygen atom of the *ortho* methoxy group could result in a simulation of part of the LSD molecule hence accounting for the hallucinogenic activity and cross tolerance of these compounds.

#### METHODS

The crystals of the free base of DOET were triclinic and the space group was  $\bar{P}1$ . The unit cell dimensions, obtained from Weissenberg photographs, were  $a=7.43$ ,  $b=16.73$ ,  $c=5.25$  Å and  $\alpha=93^\circ 30'$ ,  $\beta=87^\circ 30'$ ,  $\gamma=96^\circ 18'$ . The structure was solved by a combination of direct and Patterson superposition methods and full crystallographic details will be published elsewhere (Kennard, Giacobozzo & others, 1974).

The potential energy calculations were performed using the computer program of Motherwell (to be published) which calculates the internal energy of molecules as a function of the torsion angles defining the conformation (see Fig. 3). The method for calculation of the energy is the simple summation of atom-atom interactions using empirical functions for the Van der Waals potential (Giglio, 1969). The program produces the results in the form of a map taking any two variable parameters as axes. There is also the possibility of seeking the nearest minimum in the energy surface of many variables using a gradient (steepest descent) method. This is used to optimize the parameters after the approximate minimum position has been found by mapping. This program also enables one to examine the pattern of molecular packing in crystal structures and thus obtain an idea of the influence of these forces on the solid state conformation.

#### RESULTS

The molecular conformation of DOET is shown in Fig. 2. The free base does not appear to form any intramolecular hydrogen bonds since the distances between the

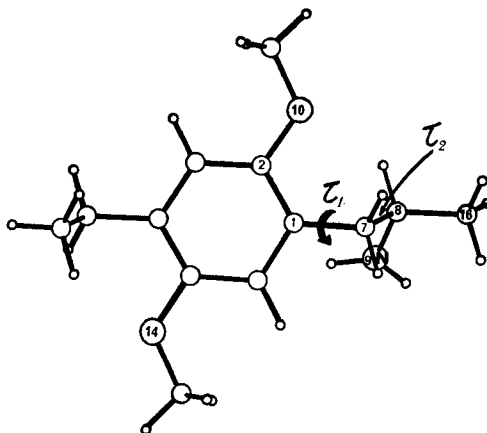


FIG. 2. A projection of the DOET molecule normal to the plane of the ring. The torsion angle  $\tau_1$  is defined as the angle between the planes of the atoms  $C_8-C_7-C_1$  and  $C_7-C_1-C_2$  i.e. for rotation about the  $C_1-C_7$  bond. Torsion angle  $\tau_2$  is the angle between the planes of the atoms  $N_9-C_8-C_7$  and  $C_8-C_7-C_1$  i.e. for rotation about the  $C_7-C_8$  bond.

amine nitrogen and the methoxy oxygen atoms are  $N(9) \dots O(10) = 4.30 \text{ \AA}$  and  $N(9) \dots O(14) = 7.13 \text{ \AA}$  whereas the expected hydrogen bonded distance is around  $2.9 \text{ \AA}$ . There is no evidence of any intermolecular hydrogen bonding. The benzene ring is planar within our experimental error. The two methoxy groups lie very nearly in the plane of the benzene ring, as has been observed in a related compound 2,4,5-trimethoxyamphetamine HCl (2,4,5-TMA) (Baker & others, 1973) Fig. 1d. The ethyl group is staggered at an angle of  $78^\circ$  and is thus similar in orientation to the 4-methoxy group in mescaline hydrobromide (Ernst & Cagle, 1973) where the corresponding torsion angle, computed from published coordinates is  $85^\circ$ . The isopropylamine side chain is staggered at a similar angle of  $-75.9^\circ$  to the plane of benzene ring. This staggering is a general feature of the whole group of phenylethylamine derivatives. The side chain is fully extended with the  $\alpha$ -methyl group anti-

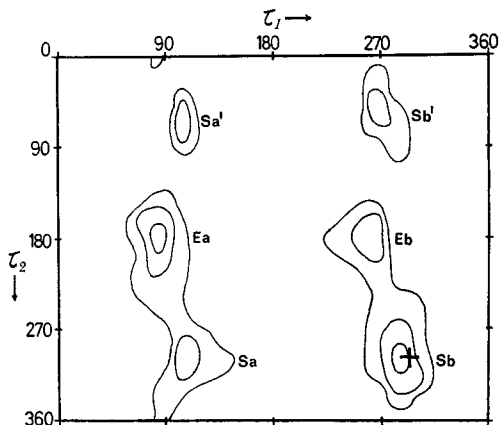


FIG. 3. A potential energy map for the various conformations of the side chain of DOET. The map was obtained through the use of a computer program which calculates the internal energy of the molecule as a function of various values of the torsion angles  $\tau_1$  and  $\tau_2$ . The position of the side chain in the crystal is marked with a cross. Contours are at  $1 \text{ kcal mol}^{-1}$  intervals.

planar ( $\tau_3 = \text{C}_{16}-\text{C}_8-\text{C}_7-\text{C}_1 = 178^\circ$ ). In this orientation the nitrogen atom assumes the synclinal position ( $\tau_2 = \text{N}_9-\text{C}_8-\text{C}_7-\text{C}_1 = -62^\circ$ ). The overall conformation of DOET is similar to that reported for the hallucinogen 2,4,5-TMA (Baker & others, 1973), and mescaline HBr (Ernst & Cagle, 1973). The results of the potential energy calculation are shown in Fig. 3. One of the conformations of minimum energy was shown to correspond to that found in the crystal, i.e. the staggered form, and is marked with a cross in Fig. 3. The map shows six minima which are related in pairs. Ea and Eb are the minima for the extended conformation in which the nitrogen atom is antiplanar, Ea being on the same side of the benzene ring as the ethyl group, while Eb is below the plane of the ring. The notation S denotes the staggered conformation in which the nitrogen atom is synclinal. Sa and Sa' are both staggered above the plane of the ring and Sb, Sb' are below the plane.

The potential energy maps for mescaline hydrochloride and hydrobromide are illustrated in Fig. 4 together with a molecular diagram showing the torsion angles varied in the calculation. The maps were computed from published molecular geometry (Tsoucaris, de Rango & others, 1973; Ernst & Cagle, 1973) and the conformations corresponding to those found in the crystal structures are marked with a cross.

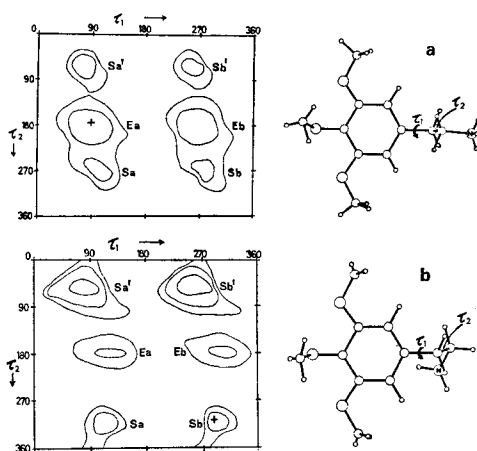


FIG. 4. Potential energy maps for (a) mescaline hydrochloride and (b) mescaline hydrobromide together with molecular diagrams showing the torsion angles  $\tau_1$  and  $\tau_2$  varied during the potential energy calculations. Published atomic coordinates were used and contours are at  $1 \text{ kcal mol}^{-1}$  intervals.

## DISCUSSION

One of the main points of interest of the present study is the demonstration that in molecules of this type the energy barriers separating the various possible conformations of the side chain are quite small, i.e. of the order of a few  $\text{kcal mol}^{-1}$  (Figs 3 and 4). The E position is the one that is most commonly found in molecules of this type (Carlstrom & others, 1973) but as indicated in these potential energy maps the staggered position is energetically equally favourable. A possible explanation of why the staggered conformation is preferred in DOET may be that here the crystal structure of the free base was examined where steric factors in the packing of the molecule in the crystal structure are more flexible than in the case of a salt, where atoms must be

in a position suitable for hydrogen bonding. This suggestion becomes less tenable, however, when one examines the X-ray structures of mescaline HCl (Tsoucaris & others, 1973) and mescaline HBr (Ernst & Cagle, 1973). In the solid state (Fig. 4) the former takes up the extended conformation and the latter the staggered position. One would, however, expect the molecules to pack in a closely similar arrangement in the two salts since the difference in ionic radii for  $\text{Cl}^-$  and  $\text{Br}^-$  is only 0.1 Å. This result does, however, emphasize once again that the energy differences for the various conformations of the side chain are very small. The suggestion that the crystal structure of 2,4,5-trimethoxyamphetamine HCl is "unusual" (Baker & others, 1973) may therefore not be valid in the light of our results and of those for mescaline HBr. No evidence for the suggested form of hydrogen-bonding (Snyder & Richelson, 1968) in this class of compounds was found in the case of DOET. As the conformation found in the crystal of DOET agreed with a minimum in the energy map for the isolated molecule it is concluded that in this structure packing forces have little effect on the conformation. The molecules are held together in the crystal structure by Van der Waals forces only. This has often been the case with other molecules already studied (Motherwell & Isaacs, 1972; Motherwell, Riva di Sanseverino & Kennard, 1973). As the energy barriers to rotation of the side chains in the molecules are so small a more direct method of obtaining information about the preferred conformation required for hallucinogenic activity is the synthesis and evaluation of carefully designed rigid analogues of this class of compounds (Cooper & Walters, 1972, Nichols, Barfknecht & others, 1974). Such information can then possibly be meaningfully related to the X-ray and theoretical studies that have been performed on the flexible compounds.

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