ing coming later at the ice-vapor interface. The internal pressure needs only to be reduced below the vapor pressure of the ice, by the superheating, for this to become possible.

Another, entirely different kind of internal melting occurs at the highest radiation intensity. Clouds of Tyndall figures grow systematically, often in planes (Fig. 1d). These clouds extend at a rate of roughly 1.5 to 2 cm/sec. The clouds consist of myriads of tiny, hexagonal water pockets, each with its own vapor bubble. Microscopic examination immediately after formation discloses no connecting channels between the pockets. The reason for the systematic growth of these clouds of Tyndall figures must lie in some sort of mechanical linkage—an effect of stress on the nucleation of new melting centers with vapor bubbles—but the details are obscure. This cloudy growth has been described before (*3*) and was explained in the same general way.

An aspect of internal melting that apparently has not been studied is the orientation of the regular melt figures (those with vapor bubbles, not the fractures). Internal melting should be analogous to ice crystal growth in supercooled water. The dendrite orientations of ice grown in supercooled water are well known to change continuously as a function of supercooling, as Pruppacher (*4*) has studied thoroughly. The melt figures, when produced rapidly, should also show variation of dendrite orientation, and, in fact, they do (Fig. 1c).

The only way to compare Pruppacher's data on ice growth with data on internal melting is to compare graphs of the growth and melting velocities plotted against the deviation angle (deviation from basal orientation) (Fig. 2). It is interesting, and puzzling, that there is almost no coincidence here. The value of the angle of deviation at a certain melting velocity is always higher than that at the same freezing velocity, and the melting data are very scattered. It may be possible to attribute this to the fact that the heating is caused by radiation, which is directional. If there is a large, direct heating effect at the ice-water interface, then the melting conditions can be very asymmetric, and the larger, and scattered, values for the deviation angle in melting may be understood.

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Molecular Structure of LSD

Abstract. *The molecular configuration of lysergic acid diethylamide (LSD) in crystals of the iodobenzoate has been determined by using x-ray diffraction techniques. The configuration shows strain and steric hindrance and the conformation is fixed. Some of the implications of this for the hallucinogenic activity of LSD are discussed.*

The molecular understanding of the biological activity of any substance requires a knowledge of its three-dimensional structure. We report here the single crystal structure analysis of lysergic acid diethylamide (LSD) *o*-iodobenzoate monohydrate and briefly discuss some implications of the results.

The crystals are monoclinic, space group $P2_1$, with unit cell parameters $a = 1421(2)$, $b = 765(1)$, $c = 1324(2)$ pm, and $\beta = 115.53(5)°$; the number

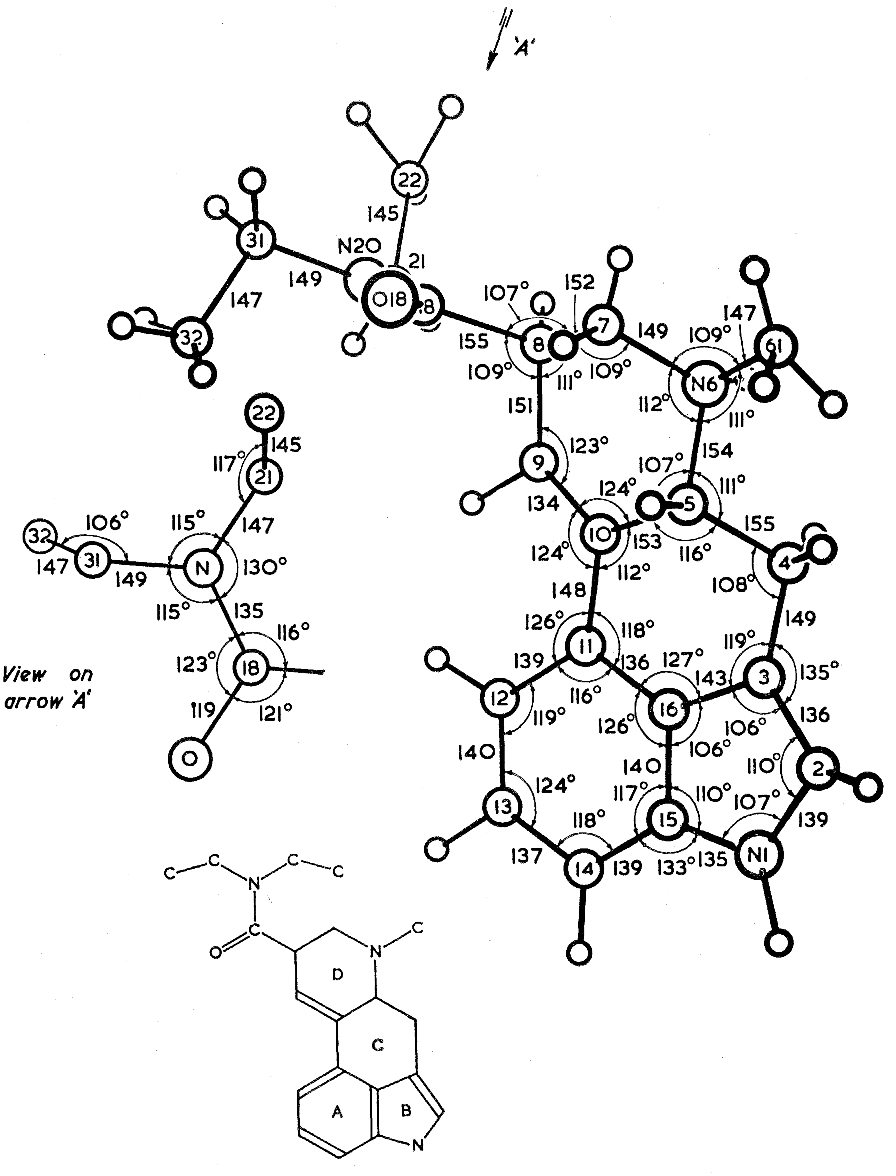

Fig. 1. The observed conformation of the LSD molecule projected onto (010). All the hydrogen positions were found experimentally. The distances and bond angles have standard deviations of 2 pm and 1°, respectively.

of molecules in the asymmetric unit $Z = 2$. Three-dimensional diffraction data were measured on a Hilger and Watts Linear Diffractometer with Mo-Kα radiation (graphite monochromator). After data reduction, 1448 unique observed diffraction data (for which the intensities I are at least three times the standard deviation of I) were used to solve the structure by heavy-atom and Fourier methods. The hydrogen atom positions were located by using difference syntheses. The structure was refined by full matrix least squares to a residual of $R = 0.039$. Anisotropic thermal parameters were used for the nonhydrogen atoms and an overall isotropic thermal parameter for the hydrogen atoms. The structure contains one molecule of water of crystallization in the asymmetric unit, and this water molecule forms hydrogen bonds to the oxygen atoms of the benzoate molecules. The observed conformation in the absolute configuration known to be that of the most potent isomer is shown in Fig. 1 projected onto the (010) plane.

The components of the anisotropic temperature factors for C22, C31, and C32 are very high and cause an apparent shortening of the C21–C22 and C31–C32 bond lengths. All other bond lengths are within 1 or 2 S.D. (S.D. = 2 pm) of their expected values.

Structural strain causes some bond angles and torsion angles to depart from their normal values. The strain can be seen as due to the different stereochemical requirements for C4 when considered as (i) a substituent in the indole ring and (ii) a substituent in the piperidine ring. The principal effect is to bend the C4–C3–C16 bond angle to 119° (S.D. = 1°) [the normal value for such substituted indoles is 127° (*1*)] and to twist the aromatic ring so that C4, C3, C16, C11, and C10 are not coplanar but form a part turn of a shallow helix (Fig. 2). The distances of these atoms from the mean plane of the indole ring are C4, −11; C3, −4; C16, −1; C11, +6; and C10, +15 pm (S.D. = 1.5 pm). This effect of ring strain on the details of the molecular structure could not be predicted from model building. The general problem of the conformation of LSD has been discussed by Chothia and Pauling (*2*), and the observed structure is very similar to that predicted.

We believe that the conformation of LSD observed in the crystal is that relevant to its activity as a potent hallucinogen. The molecule in the crystal is protonated. The pK value of N6 is 7.8 (*3*), so that at the physiological pH, 7.4, 75 percent is protonated and 25 percent is not. Ergotamine contains the lysergic acid group, and the crystal structure analyses of the compound as a free base and in its protonated form show that it has the same conformation as described above (*4*). (The similar hallucinogenic activity of phenylethylamines [pK = 9.6 (*3*)] and psilocybin [pK = 10.2 (*3*)], which are almost completely protonated at the physiological pH, strongly suggests that LSD is active in the charged form.) The unsaturated D ring is in the envelope conformation with C7 being the flap (Figs. 1 and 2). It is interesting to note that for LSD and ergotamine (both as a free base and protonated base) the flaps are on the same side, whereas in the structure analysis of 1,8-dimethyl-*d*-lysergic acid *p*-bromoanilide the flap is on the opposite side (*5*). This change of the D-ring conformation brings the acid group from an equatorial to an axial position.

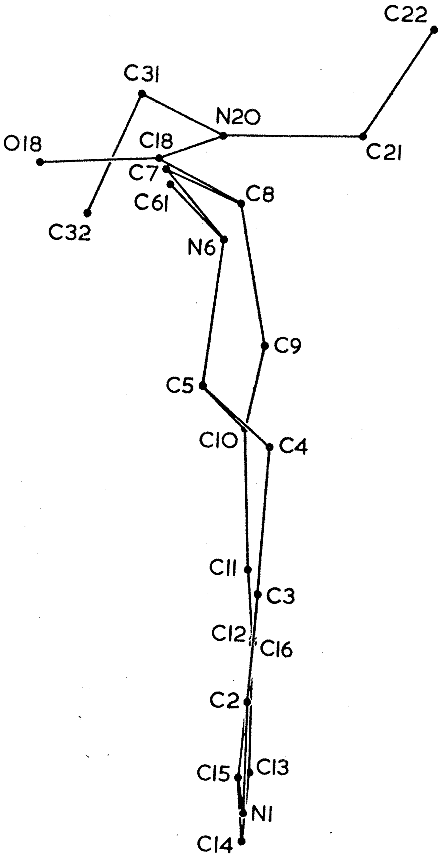

Fig. 2. The LSD molecule viewed edge on to the least-squares plane through the indole ring system. Atoms C4, C3, C16, C11, and C10 form a part turn of a shallow helix.

The atoms forming the amide group —C8, C18, O18, N20, C21, and C31—are coplanar and their mean plane is 89° to the mean of the indole ring. It is held rigidly in this position by close contacts between the amide group and the piperidine ring. The shortest of these are O18→H72 (connected to C7, above C8 in Fig. 1) (233 pm), O18→C9 (324 pm), and C21→C9 (343 pm). Replacement of one of the ethyl groups in LSD by hydrogen leads to a considerable loss of hallucinogenic activity (*6*). Replacement by hydrogen allows rotation of the amide group about C8–C18, and this would remove the short contacts just quoted. A conformation with the amide group rotated about C8–C18 relative to the position observed in the diethylamide would then be favored, reducing activity.

We have previously argued that a necessary but not sufficient requirement for the structure of hallucinogenic molecules whose effects are similar to those of LSD is a quaternary nitrogen group and an aromatic ring system in the geometrical arrangement that occurs in LSD (*2*). From the crystal structure described here we can define the relative position of the quaternary nitrogen N6 as 43 pm above the mean plane of the indole ring and 520 pm from the center of the six-membered aromatic ring. These values are a little smaller than those we predicted from model building. We believe that hallucinogenic phenylethylamines and tryptamines can adopt conformations that give a similar geometrical relationship between their quaternary nitrogen, aromatic ring, and other functional groups (*7*).

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