On the Molecular Structures of synthetic Estrogens. I. On *meso*-Hexestrol Dimethyl Ether and *trans* $\alpha\alpha'$-Bis (methylthio) stilbene

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Since several years ago a certain number of synthetic estrogens have been prepared, and a hypothesis on the reason of their efficacy was presented: they are effective because their molecular structures are closely similar to those of natural ones⁽¹⁾. In order to discuss the molecular structures of synthetic estrogens, the dipole moment of two substances, *meso*-hexestrol dimethyl ether and *trans* $\alpha\alpha'$-bis (methylthio)-stilbene, were measured. The former is an estrogenic diphenylethane, and the latter probably has the same molecular structure as that of pp'-dimethoxy *trans* $\alpha\alpha'$-bis (methylthio) stilbene, an estrogenic stilbene, because these two substances were prepared by the same reaction.

Experimental Part

The density d and the dielectric constant ε of the solutions in benzene or in carbon tetrachloride were measured with pycnometre and a heterodyne beat apparatus. The apparatus and the method used here were already reported elsewhere⁽²⁾. The wavelength used is about 150 metres.

The molar polarization P_2 of the solute was calculated by the following equation:

$$P_2=M_2\{(p_{12}-p_1)/w+p_1\},$$

where

p_{12}: the specific polarization of the solution
p_1: the specific polarization of the solvent
w: the weight fraction of the solute
M_2: the molecular weight of the solute

If $P_{2\infty}$ designates P_2 at the infinite dilution, the dipole moment at the temperature T is calculated by the equation

$$\mu=0.0127\sqrt{\{P_{2\infty}-(P_E+P_A)\}T} \quad \text{(in Debye unit)}$$

where

P_E: the electronic polarization of the compound
P_A: the atomic polarization of the compound

P_E was taken to be equal to the molar refraction MR_D for D sodium line, which was calculated by atomic refraction given in "Landolt-Börnstein Tabellen", and P_A was assumed to be 5% of MR_D. The solution, with which the experiment was carried out, were so dilute, that $P_{2\infty}$ was safely taken to be equal to the mean value of P_2's.

The solvent benzene was made free from thiophene by aluminium chloride. It was then dried over metallic sodium and distilled; the fraction boiled within 0.5°C. was collected for use. Carbon tetrachloride is the highest commercial grade, which was distilled, dried over calcium chloride and redistilled; the fraction boiled within 0.3°C. was collected for use. One of the samples *trans* $\alpha\alpha'$-bis (methylthio) stilbene, was kindly prepared by Dr. R. Ikeda of the Chemical Laboratory, Faculty of Science, Tokyo University and the other was prepared by Teikoku Zoki Co. Their purity was confirmed by the measurement of melting points: m. p. 143.9—144.0°C. for *meso*-hexestrol dimethyl ether, and 146.5—148.0°C. for *trans* $\alpha\alpha'$-bis (methylthio)-stilbene.

The results of the measurements are given in Table 1, 2 and 3.

Table 1

The Dielectric Constants and the Densities of *meso*-Hexestrol Dimethyl Ether in Carbon Tetrachloride Solutions at 25°C.

w	ε	d (g./cc.)	P_2 (cc.)
0.00000	2.2260	1.58329	—
0.00629	2.2421	1.57907	158.6
0.01098	2.2529	1.57360	162.8
0.01606	2.2632	1.56901	159.1

$P_{2\infty}=160.2$ cc. $\mu=1.77$ (D)

Table 2

The Dielectric Constants and the Densities of *meso*-Hexestrol Dimethyl Ether in Benzene Solutions at 25°C.

w	ε	d (g./cc.)	P_2 (cc.)
0.00000	2.2720	0.87236	—
0.01374	2.2861	0.87408	145.0
0.03509	2.3109	0.87736	146.6

$P_{2\infty}=145.8$ cc. $\mu=1.57$ (D)

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(1) E. C. Dodds, L. Goldberg, W. Lauson and R. Robinson: *Nature*, **141**, 248 (1938).

(2) S. Mizushima, Y. Morino and K. Higasi: *Sci. Papers Inst. Phys-Chem. Res.* (*Tokyo*), **25**, 159 (1934).

Table 3

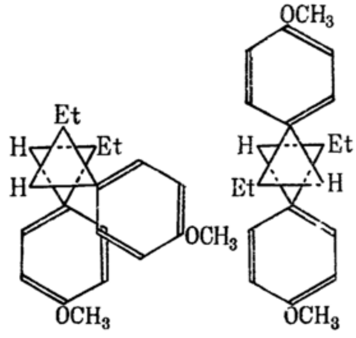
The Dielectric Constants and the Densities of *trans* $\alpha\alpha'$-Bis (methylthio) stilbene in Benzene Solutions at 30°C.

w	ε	d (g./cc.)	P_2 (cc.)
0.00000	2.2620	0.86610	—
0.01172	2.2741	0.86908	120.0
0.01531	2.2774	0.86990	118.9

$P_{2\infty}=119.5$ cc. $\mu=1.24$ (D)

Discussion of the Result

1. *meso*-Hexestrol Dimethyl Ether—As this compound has a C—C rotational axis in its center, two isomers may exist in principle with regard to this axis, the one being the trans form, and the other the gauche form, as shown in Fig. 1.



cis *trans*

$\mu=2.06$ D $\mu=1.75$ D

Fig. 1.

The dipole moments of two isomers were estimated by vector addition. For the moment of CH_3—O bond the value 1.29 D estimated from the dipole moment of hydroquinone dimethyl ether 1.70 D(3) under the assumption of the value of 111°(4) for the C—O—C bond angle was used, and for the moment of C—O bond the value 0.78 D* estimated from the dipole moment of anisole 1.35 D(5) under the same assumption. It is assumed that the methyl group makes free rotation about C—O axis. For both the moments of H—C and C_2H_5—C bonds, the value of 0.3 D was assumed. The resultant moment of the *trans* and the *gauche* form thus computed are 1.75 D and 2.06 D respectively.

On comparing them with the observed moments, the value 1.77D* observed in carbon tetrachloride solution is almost equal to that of the *trans* form. Hence it may be concluded that, if ever exist, there is only small amount of the *gauche* form in carbon tetrachloride solution. This conclusion may be justified, when taking into account the fact that in the *gauche* form two *p*-methoxyphenyl groups and two ethyl groups come mutually too near to make this form stable. The fact that this compound is of the *trans* form makes it favourable that this compound has the molecular structure similar to that of natural estrogen. The observed moment in benzene solution 1.57 D is lower than that in carbon tetrachloride solution. But the interpretation of this result seems to be difficult.

2. $\alpha\alpha'$-Bis (methylthio) stilbene—This compound has two isomers: the *trans* and the *cis* isomers with regard to the central C=C bond. The isomer used for the measurement was obtained as crystal and the other isomer remained in the solution as oil. Since these *trans* isomers generally have higher melting points than that of the *cis* isomers, the isomer used for the measurement seems to be the *trans* one. The determination whether this compound has *trans* or *cis* form is also an object of this research.

If this compound has a structure closely similar to that of natural estrogen, it must have the configuration as shown in Fig. 2.

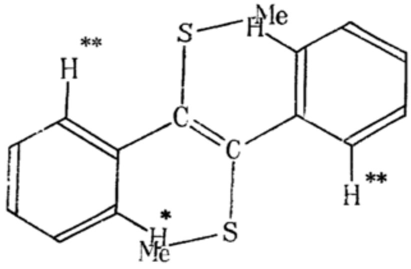


Fig. 2.

This configuration has a center of symmetry and hence has a dipole moment equal to zero. The experimental value, however, does not satisfy this expectation, so evidently this compound is not fixed in this configuration. Then the decision of the structure of this compound is interesting. At first sight it might be considered that the benzene planes are fixed on the same plane as that of the four bonds neibouring to the C=C bond by the quantum mechanical resonance between the phenyl groups and central C=C bond. But if the benzene rings are fixed on this plane, the distances between the methyl groups and the H* or H** atoms attatched to the phenyl groups at the *ortho*-positions must be shorter than 2.7 A. This distance is definitely shorter than 3.2 A., the sum of the van der Waals' radii, therefore probably the benzene rings are twisted from the plane. This conjecture agrees with the result of the ultraviolet absorption spectra of the similar compounds. The resultant moment of this molecule depends on the relative positions of the two methyl

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* For this value, from the dipole moment of phenyl ether 1.35D, (5) 0.89D is estimated under the same assumption.

(3) S. Mizushima, Y. Morino, and H. Okazaki: *Sci. Papers Inst. Phys-Chem. Res.* (*Tokyo*), **34**, 1147 (1943).

(4) R. Maxwell: *J. Opt. Soc. Am.*, **30**, 374 (1940).

(5) L. G. Groves and S. Sugden: *J. Chem. Soc.*, **1937** 1782.

groups, which can rotate around the S—C bond. Using the moment 1.15 D for CH_3—S bond, which has been obtained from the moment 1.40 D⁽⁶⁾ of dimethyl sulphide and the C—S—C bond angle 105°⁽⁴⁾, the observed value 1.24 D of this compound provides the value 112° of angle between the two S—CH_3 bonds. If both of the S—CH_3 bonds rotate in reverse directions, starting from the *trans* position as shown in Fig. 2, the positions of rotational angles 34°, 146°, and a pair of 80° and 222°, give the observed moment. Of these positions only that of the rotational angle 34° is favourable for this compound to maintain the molecular structure similar to that of natural estrogen. Assuming the values of C—C: 1.54 A., C=C: 1.34 A., C—S: 1.82 A., C—H: 1.07 A., <C=C—C: 120° and <C—S—CH_3: 105°, when the rotation by 34° around the S—C bond is assumed, the benzene rings must be twisted circa 75° from the plane, in order to keep the H* atom at the distance 3.2 A. from the methyl groups. This structure has the distances 3.12 A. between CH_3 groups and H** atoms, but the distances among the groups in a molecule generally can be shorter than the van der Waals' distances, thus probably this structure is realized.

In this place it is worth while to compute the moment of the *cis* isomer. The *cis* isomer has also the axes of rotation around S—C bonds. Assuming the moment 0.85 D for C—S bond, 1.15 D for CH_3—S bond, and 0.3 D for H—C bond, the simple vector addition gives the value from 0.40 D to 3.12 D for the moment of the *cis* isomer. But if the configurations are excluded, in which the distance between the two methyl groups is within 4.0 A., the sum of the van der Waals radii, the structure having the moment smaller than 1.30 D are not allowed to exist. The observed value 1.24 D lies in this unallowed region. Thus it might be concluded that this compound is not the *cis* isomer. But taking into account the basic assumtion for this calculation, it seems unreasonable to insist only from this reason that this compound is the *trans* isomer.

From the discussion described above it seems that these substances have general resemblance to natural estrogen in their molecular structures.

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(6) H. Staude "Physikalisch-chemisches Taschenbuch" (1945).