ENERGY OF THE HIGHEST FILLED MOLECULAR ORBITAL AND ANTISEROTONIN PROPERTIES OF DRUGS

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Hückel's method was used to calculate energy coefficient K_i of the highest filled molecular orbitals of a number of serotonin antagonists (cyproheptadine, derivatives of thiopyranoindole and dialkylindole). The results are discussed in the light of the hypotheses of Karreman et al. and of B. and A. Pullman regarding the role of electron-donor properties of drugs and their interaction with serotonin receptors.

The energy of the highest filled orbital of a substance is a measure of its electron-donor ability: the lower the energetic coefficient K_i of this orbital, the stronger the electron-donor properties of the compound [4, 11]. Investigations have shown that serotonin, and also its antagonist LDS-25, medmain, and chlorpromazine, possess low K_i values of the highest filled orbital and can form complexes with charge transfer from various electron acceptors [7, 8, 9, 12]. On the basis of these facts, Karreman has postulated [4, 8] serotonin and its antagonists, by virtue of their electron-donor properties, can form complexes (with charge transfer) with tissue receptors, and that this is related to their pharmacological action.

With this hypothesis in mind, it was decided to calculate the energetic coefficient K_i of the highest filled molecular orbital of a number of indole derivatives which, as the writers [3] have shown, possess D-, M-, and T- antiserotonin properties, and also the corresponding parameter for cyproheptadine, one of the most powerful modern serotonin antagonists of the D-type [13].

TABLE 1. Auxiliary Parameters for Atoms and Bonds*

Atom	Parameter (δ)	Bond	Parameter (δ)
C	0	C—C	1
N	1,0	C=C	0,6
S	0	C—N	0,7
—O—	2	C—S	0,9
O=	1,2	C—O	0,9
H_3	—0,2	C=O	2,0
H_2	—0,2	$C=H_3$	2,0
		$C\equiv H_3$	2,0

*As the table of parameters shows, in the model chosen 2 or 3 hydrogen atoms in a methylene or methyl group are counted as 1 atom.

EXPERIMENTAL METHOD

The calculations were made by the "simple" method of molecular orbitals in Hückel's LCAO (linear combination of atomic orbitals) approximation. The basis of the calculations was the system of parameters (Table 1) developed by B. and A. Pullman [4] and verified on a large number of different molecules. Parameters for the sulfur atom are taken from Karreman et al. (these parameters are given by Orloff and Fitts [12]).

A type BÉSM-3 digital computer was used in the investigation, with programs kindly supplied by L. A. Gribov. Since the program used to solve the secular equation was capable of minimizing the energy of not more than a 30-atom system, the molecular orbitals of compounds ALA-306 and K-281 were found by an approximate perturbation method. The perturbing effect of the dimethylaminoethyl or benzyl radicals on the strongest electron-donor level of the corresponding molecule, without a substituent at the indole nitrogen atom, was taken into consideration. The formula of the second approximation of the perturbation method for a simple structure operator [1] was used.

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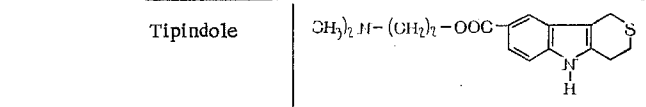
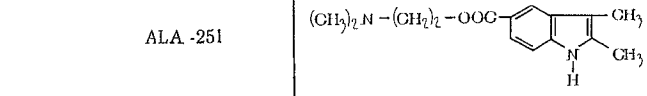
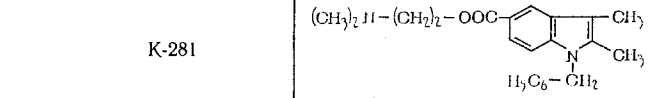
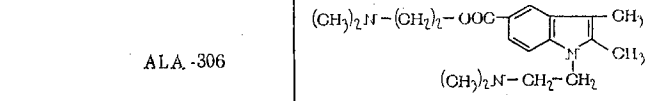
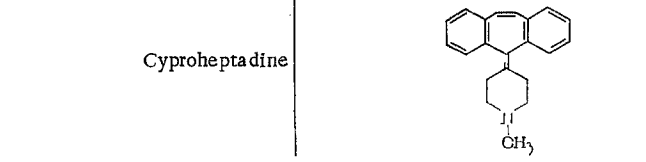
TABLE 2. Energy of Highest Filled Molecular Orbital and Antiserotonin Activity

Compound		K_i of highest filled orbitals	Antiserotonin activity					
			D-type		M-type		T-type	
name or number of compound	formula		*A_2 on rat uterus (in moles/liter)	compared with tipindole	A_2 on guinea pig's intestine (in moles/liter)	compared with tipindole	A_2 by reflex bradycardia in cats (in mg/kg)	compared with tipindole †
Tipindole		—0,091	$5,5 \cdot 10^{-6}$	1	$1,1 \cdot 10^{-6}$	1	0,35	1
K-191		—0,057	$1,34 \cdot 10^{-5}$	0,41	$1,25 \cdot 10^{-5}$	0,1	<5	>0,1
MÉA		0,507	$5,7 \cdot 10^{-6}$	0,96	—	—	<5	>0,1
ALA-251		0,535	$2,9 \cdot 10^{-6}$	1,89	$2,5 \cdot 10^{-7}$	4,4	0,38	0,75
K-281		0,519	$6,6 \cdot 10^{-8}$	83,3	$2 \cdot 10^{-7}$	5,5	0,61	0,65
ALA-306		0,520	$2,8 \cdot 10^{-8}$	196	$4,8 \cdot 10^{-6}$	0,23	2,75	0,13
Cyproheptadine		0,327		4 500	—	—	Action not specific	

*A_2 is dose (the concentration) of antagonist for which dose of serotonin must be doubled in order to obtain the same effect.

† Calculated on the basis of molecular weight.

EXPERIMENTAL RESULTS AND DISCUSSION

The structure of the compounds investigated and the results of calculations of the energy of their highest filled orbital are given in Table 2. Details of antiserotonin activity obtained previously by Pidevich et al. for indole derivatives [3], and by Stone et al. [13] and Pidevich [2] for cyproheptadine, are given on the right of the table. As Table 2 shows, cyproheptadine has a low K_i value of the highest filled orbital (0.327). The values of K_i of the highest filled orbitals of dialkylindole derivatives (ALA-251, K-281, ALA-306, MÉA) are 0.5-0.53, indicating the moderate electron-donor properties of these compounds. The highest filled orbital of the thiopyranindole derivatives (K-191, tipindole), judging from these calculations, is antibonding, because the sign of its K_i coefficient is negative. A similar property was previously described for flavins and phenothiazine derivatives [1]. It is evidence of the superdonor properties of the compounds. However, the absolute magnitude of the energetic coefficients of thiopyranindole derivatives must be accepted cautiously, for it is not yet sufficiently clear how the presence of the sulfur atom influences the calculations [4, 12]. Nevertheless, these calculations evidently show that in principle it is possible for thiopyranindole derivatives, like cyproheptadine and the dialkylindoles, to form complexes, accompanied by energy transfer, with electron acceptors.

No relationship can be observed between the energetic coefficient of the highest filled orbital of the investigated compounds and their D-, M-, or T- antiserotonin activity.

However, this fact cannot be regarded as contravening the hypothesis of the role of electron-donor properties of compounds in their interaction with serotonin receptors. It simply indicates that other characteristics of the substance are also important for this interaction. It is therefore interesting to note that, even in experiments in vitro with a combination of two substances, one of which is an electron donor, the other an electron acceptor, ability to form complexes with charge transfer was determined not only by the energy of their molecular orbitals, but also by their total charges and the arrangement of the individual atoms, the possibility of bonding and so on [5, 6, 9, 10]. In experiments on isolated organs and, in particular, in vivo, the number of factors influencing activity of the compound naturally increases. The results of these calculations cannot therefore identify the serotoninergic structures for whose interaction with the compounds the electron-donor properties of these compounds are so particularly important. The possibility is not ruled out that these properties are important for interaction with serotonin receptors of D-, M-, and also of T-types, but the selective affinity of the antagonists for receptors of a particular type is evidently due to other characteristics of their molecule.

The absolute value of K_i on the highest filled orbital does not determine whether the substance does or does not possess internal activity, i.e., the ability to produce excitation or blocking by interaction with serotonin receptors. This is shown by comparing the results of the present investigation with those obtained by Karreman et al. [10]. In fact, K_i of the highest filled orbital of the serotonin antagonists may be either higher or lower than the 0.461 characteristic of serotonin [10].

To shed further light on the mechanism of interaction of compounds with serotonin receptors, it is evidently important not only to determine the energies of the highest filled orbital, but also to obtain values for other quantum-chemical parameters of the molecule of serotonin antagonists and, in particular, their atomic charges, bond orders, free valences, and so on. Future investigations will be devoted to the calculation of these parameters.

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