A Molecular Approach to the Study of Structure-Activity Correlation for Some Amphetamines

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Abstract—Drug activity depends on both the fine as well as the gross structure of the molecule. In this work, the properties of the molecule that are dependent on its fine structure such as: dipole moment, ionization potential and energies of the HOMO and LUMO were calculated for the optimized geometry of some drugs using Ab initio method and the GAMESS program. At physiological pH, the amine part of the drug would be partially protonated, the calculations were carried out on both the charged and the free base forms. Attempts to correlate the calculated parameters to the hallucinogenic activity of the studied drugs showed that a number of correlations could be obtained. Mathematical relations between the activity and the structural parameters were derived for the studied drugs. It should be noted that the gross properties of the molecule (size, geometry and lipophilicity) are important factors in determining the drug activity.

Keywords—Ab initio, amphetamines, structure-activity

The phenylethylamine hallucinogens are simple 2-phenylethylamine derivatives of the general formula I, the majority of which are substituted with methoxy and alkyl or halogen groups (see Figure 1). When R is a methyl group, the compounds are referred to as phenylisopropylamines (amphetamines). Substitution of the phenyl group of amphetamine with one or more electron donors results in derivatives which are, in many instances, potent psychotropic agents (Shulgin, Sargent & Naranjo 1969). It has been shown that amphetamines having methoxy substituents in the 2 and 5 positons and either alkyl, alkoxy or thioalkoxy groups in the 4 position are active hallucinogens both in man and a variety of animal assays (Glennon, Liebowitz & Anderson 1980; Kier & Glennon 1978; Martin & Sloan 1977; Cheng et al. 1974; see Figure 2).

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It has been shown that a 2,4,5-trisubstituted pattern yields optimally active compounds (Shulgin 1976; Shulgin, Sargent & Naranjo 1969) in spite of the fact that some exceptions do exist. Replacement of the 4-methoxy group in mescaline with an ethoxy group gives escaline, which is about six times more active than mescaline (Braun et al. 1978).

Within the 3,4,5-trisubstituted series replacement of the 4-methoxy group with a bromine, alkyl or alkylthio group leads to compounds with high activity (Shulgin, Sargent & Naranjo 1969). In vitro assay, several 3,4,5-trisubstituted compounds showed potency comparable to similarly substituted 2,4,5 substitution patterns (Nichols & Dyer 1977). Attention has been called to the possibility of quinone generation from 2,5-dimethoxy-substituted compounds as an explanation for their high potency (Shulgin 1980a; Shulgin & Nichols 1978; Shulgin 1976; Shulgin, Sargent & Naranjo 1969). In general, the most active compounds studied to date possess 4,5-disubstitution with a

FIGURE 1
2-Phenylethylamine Derivatives

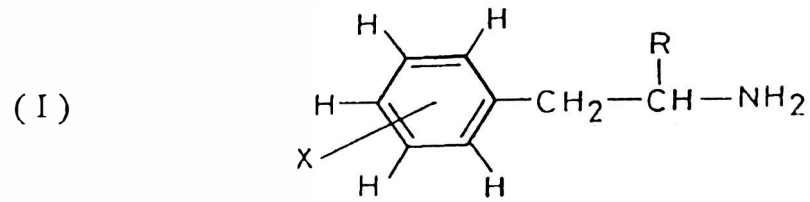
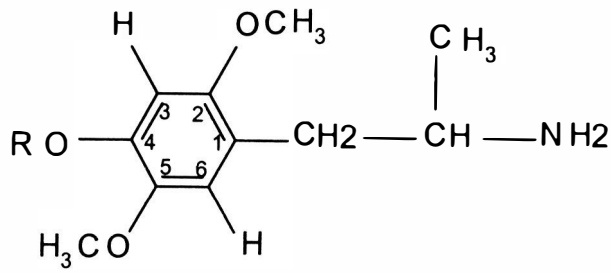


FIGURE 2
Active Hallucinogenic Amphetamine Derivatives



methoxy group at either the 2-position (2,4,5-substitution) or the 3-position (3,4,5-substitution). However, 2,4,6-trimethoxy-amphetamine possesses about 10 times the activity of mescaline in human (Shulgin 1980a).

Previous studies of physical parameters, such as charge-transfer complex stability (Sung & Parker 1972), UV absorption (Bailey & Verner 1972), and UV fluorescence (Antun & Smythies 1969) have suggested that electronic factors are relevant to the mechanism of pharmacological actions of these compounds. Molecular orbital indexes, such as the energy of the highest occupied molecular orbital (HOMO) , are sometimes successful in correlating activities of amphetamines and other psycho-active aryl-alkyl-amines (Siva Sankar 1975; Kang & Green 1970A; Snyder & Merrill 1965), but these computed quantities are dependent upon the method of calculation and the geometry of methoxy substituents (Domelsmith & Houk 1978a, b; Anderson, Castagnoli & Kollman 1978; Domelsmith, Munchausen & Houk 1977a, b, c; Anderson et al 1979). Determination of the ionization potential which is related to the energy of the HOMO, gives important information concerning the conformations of the aromatic substituents (Domelsmith & Houk 1978a, b; Anderson, Castagnoli & Kollman 1978; Domelsmith, Munchausen & Houk 1977a, b, c; Anderson et al 1979). A correlation between the ionization potentials of amphetamines and the psychotomimetic activity of these molecules in man has been attempted (Domelsmith & Houk 1978a, b; Domelsmith, Munchausen & Houk 1977a, b, c).

Comprehensive reviews of hallucinogens were presented by Brawley and Duffield (1972) and subsequently by Shulgin (1980a, b; 1976). Jacobs and Trulson (1979) presented a review on the mechanism of action for hallucinogens.

The purpose of this study is an attempt to correlate the hallucinogenic activity with the fine structure of some amphetamine derivatives (see Table 1). Some parameters of the molecular structure, namely, ionization potential (IP) energy difference (ΔE) between the highest occupied (HOMO) and lowest unoccupied molecular orbitals (LUMO) and the dipole moment (D) of the molecules were determined by molecular orbital calculations.

The human psychotomimetic activity data, relative to mescaline, reported in this work is taken from the data given

TABLE 1
The Calculated Parameters of the Free Base and Charged Amphetamine Derivatives

Number	Amphetamine Derivatives	Log Activity (log A) MU	State	Ionizaion Potential (I.P) eV	Energy Difference (LUMO -HOMO) (ΔE) au	Total Dipole Moment (D) Debye
1	2,5-dimethoxy -4-ethyl	2.000*	free base	7.670499	0.4251	1.039678
			charged	11.267661	0.4275	10.825276
2	2,5-dimethoxy -4-methyl	1.903*	freebase	7.656894	0.4269	1.040094
			charged	11.292150	0.4290	9.597792
3	2,5- dimethoxy -4-propyl	1.903**	free base	7.831038	0.4251	1.326473
			charged	11.232288	0.4279	11.517093
4	2,5- dimethoxy -4-butyl	1.602*	free base	7.779339	0.4296	1.595528
			charged	11.215962	0.4292	13.083739
5	2,5- dimethoxy -4-ethoxy	1.301*	free base	7.880016	0.4330	5.170977
			charged	10.922094	0.4319	10.830081
6	2,5- dimethoxy-4-propoxy	1.301**	free base	7.928994	0.4366	4.458793
			charged	11.166984	0.4313	12.244536
7	2,4,5-trimethoxy	1.230**	free base	7.735803	0.4283	0.679951
			charged	11.640438	0.4401	10.596814
8	2,4,6-trimethoxy	1.114*	free base	8.016066	0.4527	4.486044
			charged	11.531598	0.4473	8.530714
9	2,5- dimethoxy-3,4-methylenedioxy	1.079*	free base	8.141232	0.4441	1.722230
			charged	10.941141	0.3973	17.532756
10	6-methoxy-2,3-methylenedioxy	1.000*	free base	8.029671	0.4393	1.898302
			charged	11.575134	0.4305	9.349510
11	2,3- dimethoxy-4,5-methylenedioxy	0.698*	free base	8.236467	0.4444	1.573536
			charged	11.017329	0.4030	15.045784
12	4-methoxy	0.698**	free base	8.165721	0.4433	1.346902
			charged	11.656764	0.4240	11.841197
13	3,4- methylenedioxy	0.477**	free base	8.304492	0.4418	1.573737
			charged	11.289429	0.4013	17.101275
14	4-methoxy-2,3-methylenedioxy	0.477*	free base	8.239188	0.4596	2.039609
			charged	11.765604	0.4428	10.893775
15	3-methoxy-4,5-methylenedioxy	0.431*	free base	8.407890	0.4599	1.336310
			charged	11.297592	0.4042	17.071916
16	3,4,5-trimethoxy	0.342***	free base	8.228304	0.4559	2.154843
			charged	11.409153	0.4186	13.013421
17	2,3,4-trimethoxy	0.301*	free base	8.148874	0.4496	1.862424
			charged	11.417316	0.4440	7.561169
18	3,4-dimethoxy	-0.301**	free base	8.484078	0.4559	1.229002
			charged	11.833629	0.4305	12.419464

Note: MU = mescaline unit eV = electron volt au = atomic unit

*Nichols & Glennon 1984.

**Shulgin 1980b.

***Gupta, Singh & Bindal 1983.

TABLE 2
Total Energy of the Charged and the Free Base of Amphetamine with Different Basis Sets

Basis Sets	Total Energy Free Base	Total Energy Cation
3-21G	-400.5939648760	-400.9869574119
6-21G	-402.3776785320	-402.7700772586
6-31G	-402.6801642402	-403.0638689414

by Shulgin (1980b), Gupta, Singh and Bindal (1983), and Nichols and Glennon (1984). Activity, as is traditional for the studied substances, is measured in mescaline units (MU).

METHODS OF CALCULATION

In this work molecular orbital calculations were performed on the optimized geometry of the ground state using the *ab initio* method and relatively large basis sets. The physical parameters reported in this work are those for the optimized geometry, a geometry with the smallest total energy, where the molecule is assigned a C_1-symmetry, point group. Linear regression analyses were carried out by using the SPSS/PC (7.0) program.

The hallucinogens studied possess a basic nitrogen atom and the substituted amphetamines have pKa values of the order of ~9.4-9.8. Weinstein and colleagues (1976) suggested that an amine undergoes deprotonation upon binding and that quantum chemical calculations of the bound species must be carried out on a nonprotonated amino group. This concept has not been verified experimentally. Chothia and Pauling (1969) reported that the physiological pH of the brain is slightly higher than the blood pH and the nitrogen atom of the amine group is charged forming a quaternary ammonium ion. It is not known whether the active species is the cation or the free base. In this study both, protonated and nonprotonated forms were considered.

The equations describing the quantitative relationships between log activity (log A), dependent variable, and the calculated parameters IP, ΔE and D, independent variables, have been formulated for the studied compounds.

The total energy of the optimized geometry of amphetamine as a model was calculated using the 3-21G, 6-21G and 6-31G basis sets, the latter gave the lowest value of the total energy and hence, 6-31G basis sets were used in subsequent calculations. Results are given in Table 2.

RESULTS AND DISCUSSIONS

Quantitative structure activity relationships have been studied concerning the physical, chemical and structural properties of the molecule. The most commonly studied parameters are lipophilicity, electronic structure and steric factors. The fine structure of the molecule is expected to play an important role with respect to the activity of the molecule.

The electron-donating ability of a molecule has been related to the mechanism of the psychotropic action (Siva Sankar 1975; Kang & Green 1970a, b; Snyder & Meril 1965; Karreman, Isenberg & Szent-Gyorgyi 1959); the attachment of serotonin at receptor site in the brain has been attributed to the formation of a reversible weak molecular complex with the brain receptor (Alivistaos et al. 1971). It has been suggested that the activities of amphetamines go through the same mechanism (Sung & Parker 1972).

Energy Difference between HOMO and LUMO

The correlation between the ΔE and the activity of the free base of the studied drugs is given by the equation

log (A) = 21.184(2.956)- 45.748(6.690) ΔE

n = 18 r = 0.863 s = 0.331 F = 46.763 sig. F = 0.000

where n is the number of compounds in regression, r is the correlation coefficient, s is the standard error of estimate, and F is the variance ratio for regression model. Using the full data set, no significant correlation was found between log A and E for the protonated forms of the drugs (r = 0.152).

The hallucinogenic activity of the drug may be observed while the molecule is in the ground or excited state. In the latter case an inverse relation is expected to occur between activity of the drug and the E for the free base. Table 1 shows that higher activity is associated with a lower value of ΔE. This result means that the excited state can not be neglected as a factor which has a role with respect to the activity of the molecule.

Ionization Potential

The value of ionization potential depends on the energy of the HOMO and is related to the ability of the molecule to serve as a donor in charge transfer complexation (Mulliken & Person 1969) as well as to the reactivity of the molecule towards a variety of electrophilic reagents (Freeman 1975; Houk 1975). In this study, results shown in Table 1 indicate that there is an increase in the activity of the drugs with the decrease in its IP. The linear regression relation between the free base activity and its IP has the form

log (A) = 19.852(1.912)- 2.345(0.237) IP

n = 18 r = 0.927 s = 0.246 F = 97.529 sig. F = 0.000

No correlation was obtained between log A and IP for protonated species (r = 0.452).

Dipole Moment

It has been proposed (Sung & Parker 1972) that the mechanism of action of psychotropic drugs, mainly those with aromatic rings, may in some way be due to the electron-donating ability of these compounds. Trials to correlate the activity of the studied drugs (free base or protonated) to the dipole moment of the drugs were unsuccessful in both free base (r=0.064) and protonated (r=0.240) forms. Dipole moment is a measure of the polarity of the ground state and since a correlation between the drug activity and its dipole moment was not found, one can safely predict that the action of the drug is proceeded by excitation first. In other words, the excited state and not the ground state is the active form of the drug. This is confirmed by the existence of an inverse relation between the drug activity and ΔE.

The only undebatable fact is that the strong binding between the drug and the receptor is a requirement for a strong activity of the drug. Binding between the drug and the receptor requires a type of a charge transfer from the drug to the receptor or the formation of an ion pair between the drug and the receptor. Both of these phenomena require a polar and an easily ionized molecule which demand a special charge distribution on the molecule (excited state). As a result, one can say that compounds containing groups with a lone pair of electrons are polar, easily ionized, form stable charge transfer complexes and are active hallucinogenic compounds.

The sequence of the above factors seems to be logical, but more important than all of them is the size factor of the drug. If the molecule is polar, easily ionized and has an atom with a lone pair of electrons but is of a size and orientation that cannot fit in a space to bind to the receptor it will be an inactive molecule. This is seen on replacing the 4-methoxy group in mescaline with an ethoxy group to give escaline, which is about six times more active than mescaline (Braun et al. 1978). The replacement of methoxy group by ethoxy group will not apparently affect the charge distribution or the dipole moment or the energy difference between HOMO and LUMO of the molecule. The difference in activity between mescaline and escaline must be due to the fact that the size and orientation in space of ethoxy group fits in space and binds more firmly to the receptor than it does with a molecule with methoxy group.

CONCLUSIONS

A comparative study on the neutral and protonated amphetamine derivatives has been carried out in order to find some correlations between the fine structure of the molecule and its hallucinogenic activity. The systematic analysis presented in this work demonstrates that, for the nonprotonated forms, the structural parameters IP and ΔE are the best correlators with log A, whereas the correlation with D is nonsignificant. On the other hand, no correlation could be obtained between the studied structural parameters and log A for the protonated drugs, a result which supports the suggestion of Weinstein and colleagues (1976) that the active species is the free base of the drug. The validity of structure-activity relationships is sometimes challenged on the basis that the biological activity data used for correlation with molecular structure do not necessarily reflect the efficacy of the drug on its biological receptor, which is a composite of many events including the various stages of drug transport, uptake, metabolism and excretion. This reservation applies not only to criteria derived from theoretical studies, but also to experimental correlation such as certain physicochemical properties of the drugs.

These simple structure-activity relationships have encouraged quantitative structure activity relationships (QSARs) studies which have met with considerable success. However, since both the number and positions of substituents influence all structural and physical parameters to a large extent, it is possible not only to discover meaningful QSARs but to find meaningless ones as well.

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