Photoelectron Spectra of Psychotropic Drugs. III. Ionization Potentials and Partition Coefficients as Predictors of Substituted Amphetamine Psychoactivities

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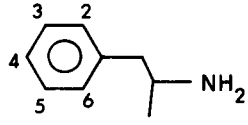
Abstract

Ionization potentials have been measured by photoelectron spectroscopy for 14 substituted amphetamines and phenethylamines. Comparisons with STO-3G calculations on various methoxylated benzene models indicate adequate agreement between calculated and experimental ionization potentials, but also reveal unexpected methoxy conformations in some of these species. Multiple regression analyses demonstrate the importance of both ionization potentials and lipophilicities, measured by 1-octanol-water partition coefficients, in determining psychotropic activities for a series of substituted amphetamines. The first and second π ionization potentials also correlate with differences in the abilities of a variety of psychotropic drugs to displace *d*-LSD from its high-affinity binding site in rat brain homogenates.

Introduction

Psychoactive drugs with aromatic moieties, such as phenethylamines, phenylisopropylamines (amphetamines) [structure (I)], and tryptamines, have been postulated to derive their activities from their basic structural topographies, including side chain conformational effects, as well as from lipophilicities and electronic characteristics such as donor abilities [1–10]. A variety of quantum-mechanical parameters designed to characterize changes in electronic structure have been cited as influential upon hallucinogenic activities [1, 2].



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While little is known about the actual chemical environment of the active site(s) to which amphetamines bind in the central nervous system, both the amino function and the aromatic ring are believed to interact with appropriate sites in the receptor [9]. The electronic structure of the aromatic system should de-

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International Journal of Quantum Chemistry: Quantum Biology Symposium 5, 257–268 (1978)

0360-8832/78/0005-0257$01.00

termine both the orientation [3, 10] and the strength of interaction in such a drug–receptor associate [8].

Information about the electronic structures of molecules, specifically their donor abilities, is available through photoelectron spectroscopy. The relationship of ionization potentials to orbital energies leads to direct comparisons between the theoretically calculated orbital energies and those provided, via Koopmans' theorem, by photoelectron spectroscopy and also permits assessment of substituent effects on individual molecular orbitals [11]. We report here the donor abilities of a variety of psychoactive drugs by photoelectron spectroscopic measurements of ionization potentials. Additional insight into the influence of substituents upon the shapes of the high-lying molecular orbitals, as well as conformations of methoxyl groups in these molecules, has been obtained by *ab initio* STO-3G calculations on these molecules, which are discussed first.

STO-3G Calculations on Polymethoxybenzenes

The two highest occupied orbitals of the methoxybenzenes, which give rise to the two lowest π ionization potentials in these molecules—and are quite similar to the two highest MOs of the methoxyamphetamines—are derived from the degenerate HOMOs of benzene, which upon reduction to C_{2v} symmetry, become b_1 and a_2 orbitals. These will be called Ph_2 and Ph_3, respectively. They are shown, along with other π MOs of benzene relevant to the later discussion, in Figure 1.

In benzene, Ph_2 and Ph_3 are degenerate and give rise to degenerate ionization

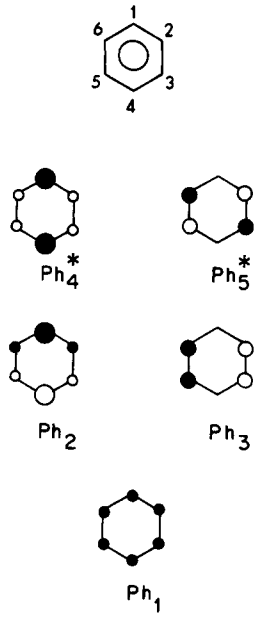

Figure 1. π molecular orbitals of benzene.

potentials of 9.25 eV in the photoelectron spectrum [12]. *Ab initio* STO-3G calculations on substituted benzenes do not reproduce energies absolutely, but do reproduce trends in orgital energies. For a variety of benzenes and substituted benzonorbornadienes, we have found a good correlation between STO-3G orbital energies ϵ_i and photoelectron ionization potentials IP_i. The correlation, which includes a few methoxy compounds and a variety of aromatics with both donor and acceptor groups, is [13]:

$$IP^c_i = -0.97\epsilon_i + 1.87$$

For benzene this equation predicts an ionization potential of 9.26 eV, very close to the experimental value. In the following discussion, the ionization potentials predicted from STO-3G calculations using this equation are identified as calculated ionization potentials IP^c. As well be seen, there is rather good agreement between calculated and experimental ionization potentials, except for the molecules containing the *o*-dimethoxy functionality. This can be taken as evidence for a different conformation of one or more methoxyl groups in these compounds, as discussed below.

Substitution by a single donor substituent splits this orbital degeneracy; the Ph_2 orbital energy is raised significantly, while the Ph_3 orbital energy remains essentially the same due to the node at the site of substitution in Ph_3. The photoelectron spectra of donor substituted aromatics, such as anisole (IP = 8.39, 9.22 eV) [14] and amphetamine (IP = 8.99, 9.35 eV) [8], show the expected shifts in IP_1 and IP_2. For anisole the STO-3G IP^c are 8.23 and 9.43 eV, respectively.

Figure 2 shows the calculated ionization potentials of various methoxylated benzenes, along with experimental ionization potentials of relevant methoxylated benzenes, phenethylamines, and amphetamines. The calculations assumed the so-called "planar" conformation of the methoxyl group, which has the CO bond coplanar with the benzene ring. The methyl was staggered with respect to the O—C(aromatic) bond with the dihedral angle C(aromatic)OCH equal to 180°, while the aromatic ring was held in the benzene geometry. Standard bond lengths and angles were assumed for the aromatic ring. Bond lengths and angles for the methoxyl substituents were taken from x-ray data for trimethoprim, where three contiguous methoxyls are present; the outer two are planar, and the central is "perpendicular" [15].

We first discuss the STO-3G predictions. In *p*-dimethoxybenzenes the split caused by one methoxy group in anisole is exacerbated, with the second methoxyl group having about 70% as large an effect as the first. If a first-order model were to hold, where the extent of orbital energy raising is proportional to the coefficients at the site of substitution, *meta*- and *ortho*-dimethoxybenzene would have identical first and second ionization potentials, since in both cases the HOMO arises from disubstitution of Ph_3 and the SHOMO arises from disubstitution of Ph_2 at sites of identical coefficients in each case. However, the calculations indicate that the HOMO of the *ortho*-disubstituted compound is substantially higher in energy than that of the *meta,* while the SHOMO of the *ortho* compound is lower than that of the *meta.* The explanation for this difference lies in higher-order effects [16], discussed below.

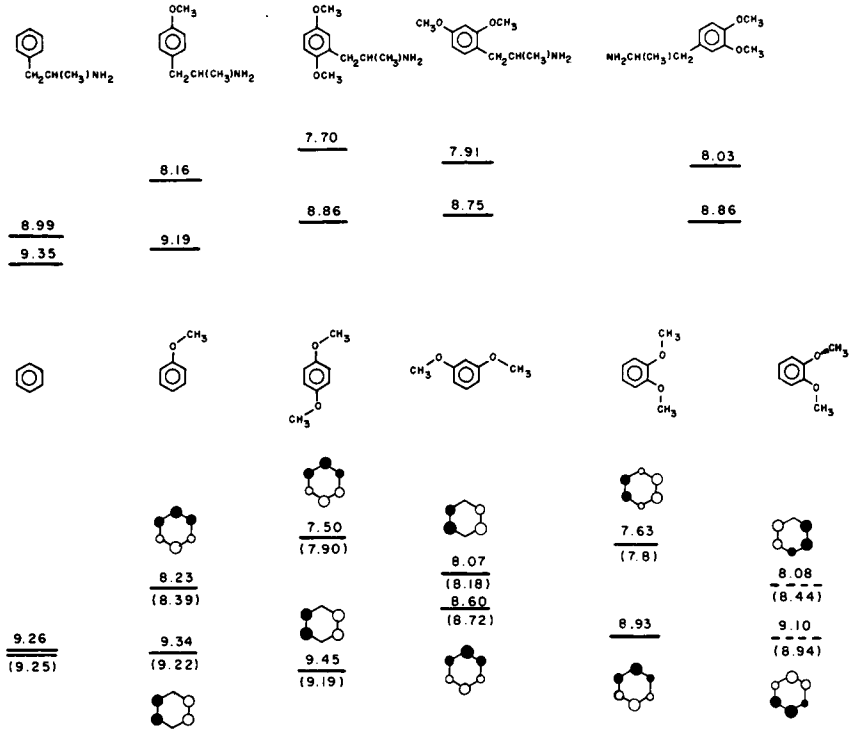

Figure 2. Experimental ionization potentials of mono- and dimethoxyamphetamines and calculated ionization potentials of methoxylated benzenes. Experimental ionization potentials for the methoxylated benzenes are in parentheses.

After first-order mixing of Ph_3 with the methoxy lone pair orbitals, the HOMO of *meta*-dimethoxybenzene will consist of Ph_3 mixed in an antibonding fashion with an antisymmetric combination of oxygen lone pair orbitals. Ph_5^* is the only other aromatic orbital of the same symmetry species, a_2, in the C_{2v} point group, and Ph_3 and Ph_5^* will mix to a small extent, lowering the energy of Ph_3. We might say that the oxygen lone pair orbitals have "caused" this mixing. The polarization of the HOMO in the full calculation (Fig. 2) is clearly a result of this mixing, with Ph_5^* mixing into Ph_3 in a negative fashion at the site of methoxy substitution [16]; that is, the HOMO coefficients are decreased at the site of substitution, and increased at the remote positions. We will call this effect polarization *away* from the substituents. By contrast, the SHOMO, which is related to Ph_2, is of the correct symmetry, b_1, to mix both with Ph_1, which will raise Ph_2 and polarize Ph_2 *toward* the substituents, and with Ph_4^*, which will lower Ph_2 and polarize it *away* from the substituents. The calculations indicate that the influence of Ph_1 is dominant, both because Ph_2, now the SHOMO, is higher in energy than expected, and because this orbital is polarized *toward* the substituents.

In *ortho*-dimethoxybenzene, the situation is opposite. Here the HOMO, Ph_3, is of correct symmetry, b_1, to interact with both Ph_1 and a vacant orbital, Ph_4^*, while the SHOMO, which is of a_2 symmetry, is lowered by interaction with Ph_5^*,

but unaffected by Ph_1. Once again, this can be seen in the different polarization of the HOMO and SHOMO of *ortho*-dimethoxybenzene.

Turning to the trimethoxybenzenes, there is a dramatic difference between the 1,2,4-compound on the one hand and the 1,2,3- and 1,3,5-compounds on the other. The 1,3,5-trimethoxybenzene has local C_{3h} symmetry, so that the HOMO and SHOMO are nearly degenerate, and both are raised approximately to the same extent as the HOMO of *meta*-dimethoxybenzene. This is as expected on the basis of the first-order analysis, since substitution of the third methoxyl, which converts *meta*-dimethoxybenzene to 1,3,5-trimethoxybenzene, occurs at a nodal position in the HOMO of the *meta* compound. A first-order analysis, based on the benzene MOs would predict the same orbital energies in the 1,3,5- and 1,2,3-trimethoxybenzenes. However, the slightly higher orbital energies in the 1,3,5-compound are a result of the smaller donor effect of the middle 1,2,3-trimethoxybenzene methoxy group, which, by necessity, has a perpendicular conformation and is, therefore, a poorer donor. Finally, the large split in the 1,2,4-trimethoxybenzene HOMO and SHOMO results from the dominant influence of the *para*-dimethoxy pattern, which is present only in this trimethoxybenzene. In effect, all three methoxys raise the HOMO energy, while only one, the 2-methoxy, raises the SHOMO energy.

Turning to the comparison between the calculated and experimental ionization potentials, there is adequate agreement for benzene through the dimethoxybenzenes, except for the dramatically higher experimental first ionization potential of *ortho*-dimethoxybenzene. Thus the experimental ionization potential is 0.8 eV higher than predicted and is higher than that of *meta*-dimethoxybenzene. The photoelectron spectrum of *ortho*-dimethoxybenzene has a small shoulder at 7.8 eV. This low-energy shoulder indicates the presence of a minor conformer, which, because of its lower ionization potential, could be the all planar isomer. STO-3G calculations on an *ortho*-dimethoxybenzene, which has one of the methoxyls rotated out of the molecular plane by 90°, show a large decrease in HOMO energy ($\Delta IP^c = 0.46$ eV), placing this orbital at the same energy as the HOMO of *meta*-dimethoxybenzene. There is a smaller decrease ($\Delta IP^c = 0.18$ eV) in SHOMO energy. Thus calculations indicate that the unexpectedly high experimental ionization potential of *ortho*-dimethoxybenzene arises from a conformation in which one or both of the methoxy C—O bonds are rotated out of the plane of the aromatic ring.

The mono- and dimethoxyamphetamines have ionization potentials quite similar to those of the corresponding benzenes, except that the alkylamino side chain lowers the first and second ionization potentials somewhat. Nevertheless, the effectiveness of the *p*-dimethoxy unit in lowering the ionization potential is clearly seen: the 2,5-dimethoxy and 4-methyl-2,5-dimethoxyamphetamines have much lower ionization potentials than *m*- or *o*-dimethoxy cases.

The conversion of benzene to amphetamine lowers the first ionization potential by 0.33 eV and leaves the second one unaffected [8]. Similarly, in 4-methoxy-, 2,4-dimethoxy, and 3,4-dimethoxyamphetamine, the first ionization potential is 0.3–0.4 eV lower than that of the corresponding dimethoxybenzene. In each of these cases, the alkylamino side chain is *para* to one methoxy substituent, and

the change in ionization potentials indicates that the HOMO becomes Ph_2-like (Fig. 1) with alkylamino and methoxy substituents at C-1 and C-4, while the SHOMO is Ph_3-like.

Upon conversion of 1,4-dimethoxybenzene to 2,5-dimethoxyamphetamine and upon conversion of the latter to the 4-methyl derivative (DOM), the second ionization potential is influenced twice as much as the first. This is indicative of the dominant influence of the *p*-dimethoxys in orientation of the HOMO and SHOMO. These two methoxys are on C-1 and C-4 (Fig. 1) so that further substitution has a larger effect on Ph_3 than Ph_2.

The comparison between 4,5-dimethoxyamphetamine and 4,5-methylenedioxyamphetamine is also an interesting one, since the first ionization potentials are almost identical, but the second one is 0.1 eV higher in the latter compound. Thus one planar and one perpendicular methoxy seem to influence the ionization potentials to an extent similar to that of one methylenedioxy group.

The trimethoxybenzene calculations are compared to the experimental ionization potentials of trimethoxybenzenes and amphetamines in Figure 3. Photoelectron ionization potentials for 1,2,4-trimethoxybenzene are not available; however, the ionization potentials for 1,2,3- and 1,3,5-trimethoxybenzene are in good agreement with the calculated ionization potentials, which predict that the first and second ionization potentials will be close in energy and that the ionization potentials of 1,3,5-trimethoxybenzene will be slightly lower than those of 1,2,3-trimethoxybenzene. The photoelectron spectra of the 1,2,3- and 1,3,5-trimethoxybenzene each show a single broad band at 8.29 and 8.15 eV, respectively, which is assigned to ionization from both Ph_2 and Ph_3 in each case.

The calculated ionization potentials of the trimethoxybenzenes agree qualitatively with the photoelectron ionization potentials for the corresponding trimethoxyamphetamines. As in the previous cases, the alkylamino side chain is a rather small perturbation on the π system of aromatic moiety as compared to the methoxy groups. The decrease in first and second ionization potentials on going from 1,2,3-trimethoxybenzene (both at 8.29 eV) to the corresponding 2,4,6-trimethoxyamphetamine (7.76 and 8.19 eV) is attributed to the greater influence of the isopropylamino substituent upon the b_1 orbital. The split between the first and second ionization potentials for 2,4,6-trimethoxyamphetamine also results from the loss of C_{3h} symmetry on addition of the isopropylamino substituent to 1,3,5-trimethoxybenzene; the much lower first ionization potential is consistent with the ubiquitous *"para* effect" in this series.

There is, however, a moderately large discrepancy between the first experimental ionization potential of 2,4,5-trimethoxyamphetamine and the calculated ionization potential of 1,2,4-trimethoxybenzene. As with *ortho*-dimethoxybenzene, this discrepancy may arise from nonplanarity of one or more methoxys.

The *para*-dimethoxy pattern, in both the di- and tri-substituted amphetamines, is particularly effective in lowering the first ionization potential. It is probably more than a coincidence that this pattern is also present in the most potent amphetamine hallucinogens (see later).

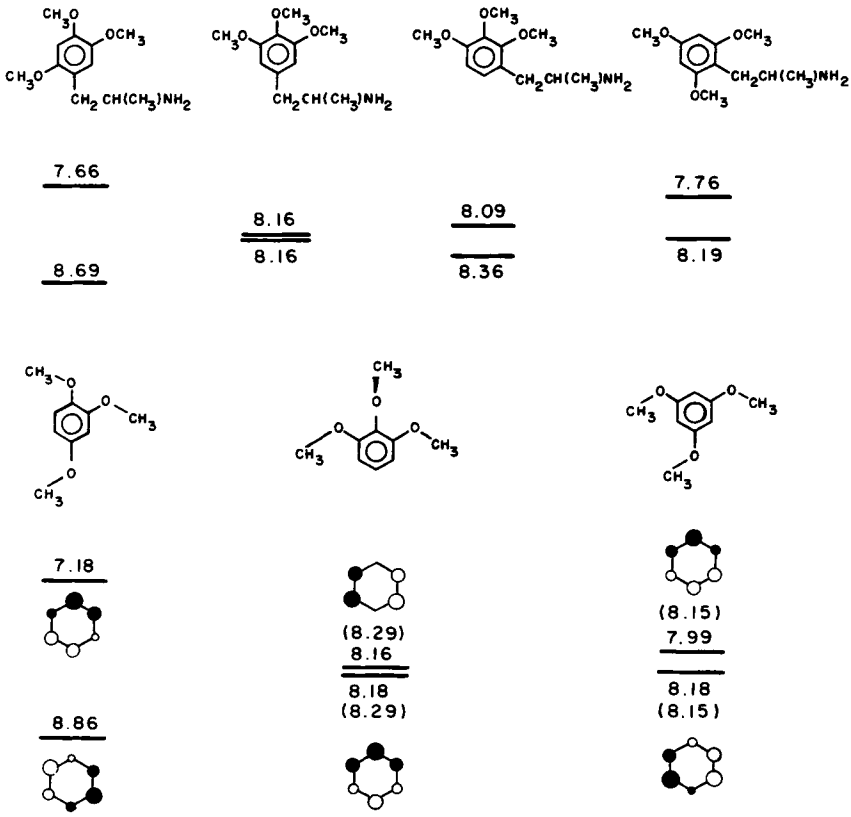

Figure 3. Experimental ionization potentials of trimethoxyamphetamines and calculated ionization potentials of trimethoxybenzenes. Experimental ionization potentials for the trimethoxybenzenes are in parentheses.

As can be noted from calculations or the experimental data, successive addition of methoxy groups to the benzene ring lowers the aromatic ionization potential, but the effect is rapidly attenuated. This results from a number of effects. First, the ionization-potential-lowering influence of the methoxy donor depends both on the coefficient at the site of substitution and inversely on the difference in energy between the aromatic π orbital and the oxygen lone pair orbital. As methoxys are added, ring coefficient sizes decrease and the energy gap increases. Second, polysubstitution will require one or more of the methoxys to assume the perpendicular conformation, which is less favorable for electron donation, or the increasing of orbital energies. Thus tetra- and penta-methoxyamphetamines are not expected to have appreciably lower ionization potentials than 2,4,5-trimethoxyamphetamine.

The photoelectron spectra of 2,5-dimethoxyamphetamine and several of its 4-substituted derivatives are shown in Figure 4. The first band falls near 7.6–7.7 eV for 4-methyl-, and 4-thiomethoxy-, and the parent 2,5-dimethoxyamphetamine, indicative of the major role of *para*-methoxyl groups in lowering the first ionization potential. The effect of the 4-substituents in lowering the second

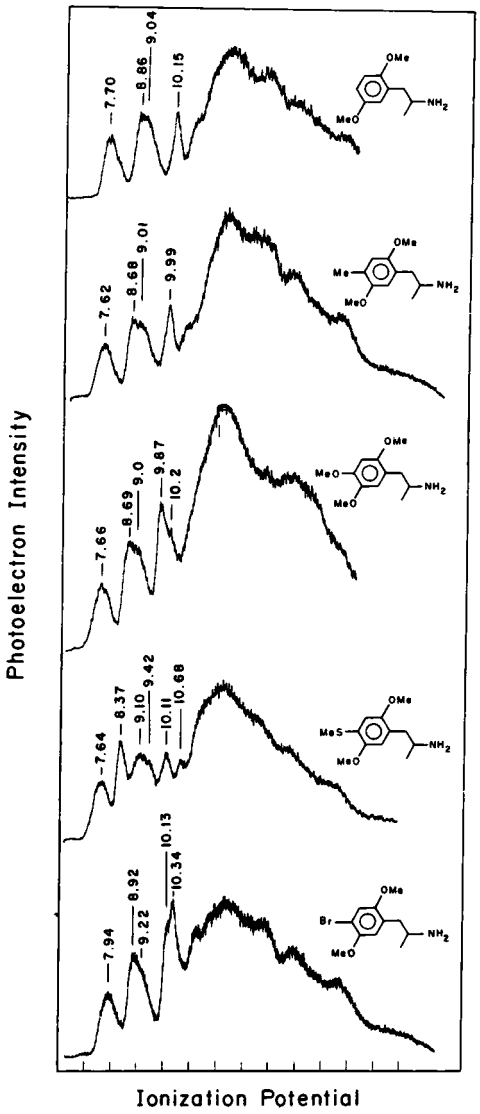

Figure 4. Photoelectron spectra of 2,5-dimethoxy-, 4-methyl-2,5-dimethoxy-, 2,4,5-trimethoxy-, 4-thiomethoxy-2,5-dimethoxy-, and 4-bromo-2,5-dimethoxyamphetamine.

π ionization potential is greater, particularly in the case of the 4-thiomethoxy derivative, where considerable sulfur character is mixed into the aromatic π orbitals, giving rise to several relatively low-energy ionization bands. Both IP_1 and IP_2 for 4-bromo-2,5-dimethoxyamphetamine are raised by the presence of the inductively withdrawing bromine substituent. The ionization potentials for the nitrogen lone pair of the isopropylamino side chain falls consistently near 9.0–9.1 eV, indicating little or no interaction between the side chain amino group and the aromatic π system. The broad amine lone pair ionization band and the

second aromatic π ionization band frequently overlap in the photoelectron spectra of substituted amphetamines producing a broad low-energy envelope. Although IP_1 and IP_2 are given to two decimal places, the accuracy frequently is not expected to be greater than 0.1–0.2 eV. Higher ionization bands in the 9–11 eV region are assigned as oxygen lone pair ionizations. The sigma envelope obscures the remaining aromatic π ionization band.

IP_1 and IP_2 for a series of substituted amphetamines and other psychotropic drugs involved in this study are listed in Table I. A general trend of decreasing ionization potential with increasing donor substitution is observed [8, 17]; increasing donor substitution also correlates, although very roughly, with increasing hallucinogenic activity, where hallucinogenic activities are measured in molar mescaline units (MMU) [18]. Several of the substituted amphetamines have similar first ionization potentials but differ significantly in hallucinogenic activity. For example, dopamine (3,4-dihydroxyphenethylamine), which has an IP_1 essentially identical to that of 4-methoxyamphetamine or 3,4,5-trimethoxyamphetamine, has no hallucinogenic activity. Similarly, the greater activity of 4-methoxyamphetamine (3.9 MMU) over 3,4,5-trimethoxyamphetamine (2.1 MMU) is not explained by ionization potentials. Clearly, other factors such as differences in transport, metabolic stability, and steric effects, play important roles in determining the hallucinogenic activities for a series of closely related drugs.

Barfknecht, Nichols, and Dunn have successfully used octanol–water partition coefficients P to predict hallucinogenic activities for substituted amphetamines, where log P is presumed to be a membrane permeability parameter [7]. The greater activity of 4-methoxyamphetamine (log P = 1.77) over 3,4,5-trimethoxyamphetamine (log P = 1.48) is accounted for by the greater lipophilicity of the 4-methoxy derivative. A multiple regression analysis of hallucinogenic activity data for substituted amphetamines, (6)–(10) and (12)–(17), with respect to ionization potentials and log P, generates the correlation equation [19]

$$\log \text{MMU} = -1.48\ IP_1 + 0.78 \log P + 11.15 \qquad (n = 11, r = 0.94)$$

The agreement is good for all amphetamines in this study with established hallucinogenic activities except for 4-bromo-2,5-dimethoxy-amphetamine. The unusually high activity (519 MMU) of this amphetamine is not predicted by ionization potentials or log P and necessitates an extensive study of halogenated amphetamines in order to determine the source of this unusually high activity.

The significance of ionization potentials in predicting the strength of drug-receptor interactions is reinforced by good correlations between ionization potentials and the ability of a psychotropic drug to displace specifically bound *d*-LSD from rat brain homogenates. For example, the effective dose necessary to displace 50% of the specifically bound *d*-LSD, ED_{50} [20], for the drugs chlorpromazine, promethazine, *N,N*-dimethyltryptamine, 4-methyl-2,5-dimethoxyamphetamine, mescaline, dopamine, and LSD is related to their corresponding π ionization potentials by the equation [17, 19]

$$-\log ED_{50} = -2.79\ IP_1 - 1.93\ IP_2 + 43.26 \qquad (n = 7, r = 0.97)$$

TABLE I. Photoelectron π ionization potentials of psychotropic drugs.

No.	Amphetamines	π IP_1	π IP_2	Reference
1	Parent	8.99	9.35	8
2	2-MeO[1]	8.24	8.93	14
3	3-MeO[1]	8.28	8.93	14
4	2,3-diMeO[1]	8.30	8.72	This work
5	2,6-diMeO	8.18	8.18	This work
6	4-MeO[2]	8.16	9.19	8
7	3,4,5-triMeO	8.16	8.16	This work
8	2,3,4-triMeO	8.09	8.36	This work
9	3,4-diMeO[2]	8.03	8.86	8
10	3,4-Methylenedioxy	8.01	8.97	This work
11	4-Br-2,5-diMeO	7.94	8.92	This work
12	2,4-diMeO	7.91	8.75	This work
13	2,4,6-triMeO	7.76	8.19	This work
14	2,5-diMeO	7.70	8.86	This work
15	2,4,5-triMeO	7.66	8.69	This work
16	4-MeS-2,5-diMeO	7.64	8.37	This work
17	4-Me-2,5-diMeO	7.62	8.68	This work
	Others			
	Mescaline	8.18	8.18	8
	Dopamine	8.18	8.90	This work
	Tryptamine	7.69	8.25	8
	N,N-Dimethyltryptamine	7.57	8.22	8
	5-Methyltryptamine	7.64	8.03	8
	5-Methoxytryptamine	7.68	7.79	8
	LSD	7.25	8.04	8
	Promethazine[3]	7.20	8.26	21
	Chlorpromazine	7.16	8.25	21

[1] Ionization potentials estimated from those of corresponding toluenes.
[2] Ionization potentials estimated from those of corresponding phenethylamines.
[3] Ionization potentials estimated from those of promazine.

Similarly, Green and coworkers have determined inhibition constants for high-affinity *d*-LSD binding, IC_{50}, in rat brain homogenates for the drugs *d*-LSD, tryptamine, 5-methyltryptamine, 5-methoxytryptamine, 2,4-dimethoxyamphetamine, 2,5-dimethoxyamphetamine, 2,4,5-trimethoxyamphetamine, 2,4,6-trimethoxyamphetamine, 3,4,5-trimethoxyamphetamine, and mescaline [3]. The relationship between IC_{50} and ionization potentials is given by [19]:

$$-\log IC_{50} = -3.18\ IP_1 - 1.64\ IP_2 + 47.78 \qquad (n = 10, r = 0.85)$$

These correlations emphasize the importance of electronic structure, particularly donor abilities measured as photoelectron ionization potentials, in drug–activity relationships. Refinements in electronic structure parameters, such as orientational effects, may lead to improved quantitative structure–activity predictions. Studies into the electronic characteristics of drugs and drug–receptor models are continuing in our laboratories.

Acknowledgment

This work was supported by the National Institutes of Health under research grant GM-21311. The authors are grateful to Dr. D. E. Domelsmith for assistance on statistical aspects of this work.

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Received March 15, 1978
Revised May 1, 1978