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(36) Impurities in the dye samples can also give rise to errors. For these time scales and concentrations the errors are usually not caused by diffusion or excitation transfer but by the contribution impurities make to the fluorescence data. For example, if the impurity is not so highly halogenated as the pure compound, it will very likely have a longer fluorescence lifetime and a higher quantum yield. The higher quantum yield will cause the impurity to contribute disproportionately to the decay curve. An apparently longer lifetime will thus be measured than for the pure compound. [We acknowledge Dr. Ken Spears, Northwestern University, for a discussion about this point.] While precautions were taken (section IIa) to avoid impurity effects, there is always a possibility that some error can arise from this source because of the very impure state of commercially available fluorescein derivatives. The lifetimes reported in this paper are generally shorter than those reported in our earlier work.[11] We do not know whether this is because we have gained more familiarity with the impurity problems in these molecules and are now better qualified to avoid them or whether the more complex analysis in the earlier work together with noisy data led to greater errors than expected.

Photoelectron Spectra of Psychotropic Drugs. 1. Phenethylamines, Tryptamines, and LSD

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Abstract: A number of correlations between calculated highest occupied molecular orbital (HOMO) energies and psychotropic activity have been reported in the literature. In order to determine whether any correlation between experimental ionization potential and drug activity exists, as well as to learn more about the electronic structures of these systems, the photoelectron spectra of phenethylamine and ten substituted derivatives or analogues, of tryptamine and seven derivatives or analogues, and of LSD have been measured. Photoelectron spectral data are given for phenethylamine, *N*-methylphenethylamine, *N,N*-dimethylphenethylamine, 4-hydroxyphenethylamine, 4-methoxyphenethylamine, 3,4-dimethoxyphenethylamine, mescaline, *N*-methylmescaline, γ-phenylpropylamine, amphetamine, methamphetamine, tryptamine, *N*-methyltryptamine, *N,N*-dimethyltryptamine, gramine, 5-methyltryptamine, 5-methoxytryptamine, 5-methoxy-*N,N*-dimethyltryptamine, and lysergic acid diethylamide (LSD). Model compounds, 3,4-dimethoxytoluene and 3,4,5-trimethoxytoluene, have also been studied. The changes in ionization potentials in these series have been interpreted in terms of the influence of substitutions on the molecular orbital energies of these molecules. Although only limited biological data are available, it is shown that not only the first IP, which is not always affected much by substituents, but also the second IP, must be taken into account in order to correlate activity with ionization potentials. The use of this average is justified theoretically, in terms of perturbation, or charge transfer, models of reactivity, as well as empirically.

In 1959, Karreman, Isenberg and Szent-Györgi observed that a number of drugs, including LSD, have unusually high energy highest occupied molecular orbitals (HOMO's), according to approximate calculations.[2] Since that time, a number of correlations between the HOMO energy of a molecule, calculated by various approximate techniques, and the pharmacological activity of the molecule, measured in a variety of ways, have been found.[3] These correlations have been interpreted as evidence for the importance of electron donation or charge transfer from the molecule to an acceptor moiety at the active site. In some tests, correlations between calculated HOMO energies and activities have not been found.[3b]

Phenethylamines with one or more donor substituents on the benzene ring, and tryptamines with simple or elaborate (e.g., LSD) substituents, are the classes of molecules for which correlations between HOMO energies and activities have been most frequently postulated. Psychotomimetic or hallucinogenic activity in man, or some more or less suitable animal model for hallucinogenicity, is the type of activity with which the electron-donor property of these drugs has been correlated.[4]

The ability of the drug to act as an electron donor is not, of course, the only feature required for hallucinogenicity. An aminoethyl side chain or alkylamino group able to assume a molecular location relative to the aromatic ring similar to that found in LSD is optimal for activity,[5] and N-alkylation helps protect the side chain against deactivation by monoamine oxidase.[6] It has also been proposed that the protonated amino side-chain hydrogen bonds to a phosphate moiety of an ATP residue, and the aryl moiety then acts as a donor in an electron donor-acceptor complex elsewhere in the active site.[7,8] Whatever the details of drug-receptor interaction, even a casual inspection of the structures of hallucinogens leaves no doubt that the electron donor ability of the aromatic portion of the molecule must be important in conferring hallucinogenic properties on certain phenethylamines and tryptamines.

Correlations between HOMO energies and activities are, of necessity, based on calculated orbital energies, because orbital energies are merely artifacts, if extraordinarily useful ones, of the Hartree-Fock-Roothaan formalism. The physical property of a molecule which correlates most closely with its HOMO energy is its lowest ionization potential (IP). Koopmans' theorem states that the negatives of the orbital energies of a molecule are equal to the ionization potentials of the molecule:[9]

$$-\epsilon_i^{SCF} = IP_i$$

Although this approximation is known to suffer from severe limitations, it is common practice to discuss IP's in terms of

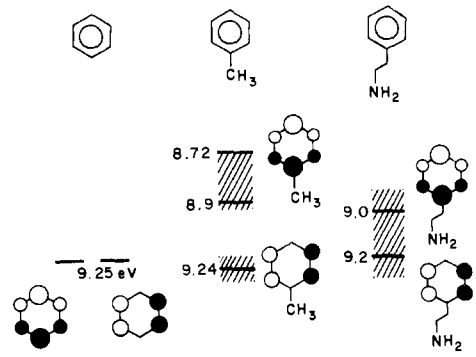


Figure 1. Molecular orbitals of benzene, toluene, and phenethylamine. The circle diameters represent coefficient magnitudes. Horizontal lines are vibrational maxima in each band. Shaded area represents bandwidths.

the orbitals which are vacated upon ionization, as a first approximation.

While a variety of calculational techniques reproduce trends in IP's, most calculational techniques are incapable of quantitative IP predictions. Furthermore, certain assumptions about geometry are generally made in order to carry out these calculations economically, but predicted IP's are quite sensitive to the molecular geometry and conformation chosen for the calculation, as shown later.

The IP of a molecule is related both to the ability of the molecule to serve as a donor in charge-transfer complexation[10] and to the reactivity of the molecule toward a variety of electrophilic reagents.[11] Thus, the IP's of molecules are not only experimentally determinable, but are fundamental indices of the reactivities of these molecules.[12]

In order to determine whether an experimental measure of donor ability, the IP, of the phenethylamines and tryptamines correlates with hallucinogenic activity, as well as to elucidate the details of the electronic structures of phenethylamines and tryptamines, we have carried out photoelectron spectroscopic studies of a variety of active and inactive molecules in these series.

Experimental Section

Photoelectron spectra were recorded on a Perkin-Elmer PS-18 spectrometer using the He I (21.21 eV) source. Resolution was 20–30 meV at 15.76 eV. Peak positions were calibrated by simultaneously recording the spectra of the calibrants, xenon and argon, along with that of the sample. Vertical IP's were taken as the position of maximum intensity, or, for ionizations having several vibrational bands of nearly equal intensity, the average of these peak positions. The reported vertical IP's are averages of four to five individual determinations.

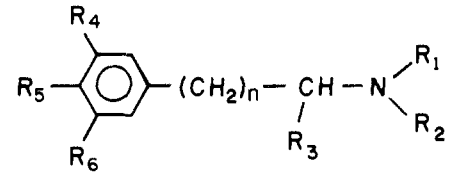
Results

Phenethylamine Molecular Orbitals. Phenethylamine has three low-energy IP's, arising from three high-lying MO's; two are more or less localized on the aromatic ring, and one is identifiable as the amine lone pair. Substituents with high-lying lone pairs or π orbitals will have additional low-energy ionizations. The energy of the nitrogen lone pair (n_N) ionization will be mainly influenced by substitution on nitrogen or the side chain, while substituents on the aromatic ring, which seem to influence phenethylamine activities most, will mainly influence the IP's of the aromatic moiety.

In benzene, the degenerate (e_{2g}) HOMO's give rise to an IP of 9.25 eV,[13] but this degeneracy is lifted by monosubstitution. Thus, toluene has IP's of 8.72 and 9.24 eV, due to ionizations from the b_1 and a_2 orbitals, respectively.[14] As shown in Figure 1, the b_1 orbital is symmetric with respect to the vertical plane in the assumed C_{2v} point group, while the a_2 is antisymmetric and has a node at C-1. We will refer to these orbitals as Ph_s and Ph_a, respectively. Methyl substitution raises Ph_s by 0.53 eV from its energy in benzene through hyperconjugation, while Ph_a is virtually unchanged. The much smaller effect of methyl substitution on Ph_a than on Ph_s is expected because the conjugative effect of a group upon the Ph orbitals is approximately proportional to the square of coefficient in the phenyl orbital at the site of attachment.

The aromatic orbitals of phenethylamine are quite similar to those of toluene, as are the IP's, as discussed in the next section. Substitution of an aminomethyl group for hydrogen has a minor effect on the ability of the side chain to hyperconjugate with the benzene ring. An important consequence of this is that IP's of substituted toluenes serve as excellent models for the IP's of substituted phenethylamines. On the other hand, any significant differences between the IP's of a phenethylamine and its toluene analogue would be indicative of specific side-chain through-space interactions with the aromatic ring, which have been postulated as important in producing a conformation mimicking that of LSD.[5]

PES of Phenethylamines. Spectral data for the phenethylamines **1–11** are recorded in Table I and Figures 2 and 3. Of this series, β-phenethylamine (**1**), γ-phenylpropylamine (**9**),



	R_1	R_2	R_3	R_4	R_5	R_6	n
1							1
2	Me						1
3	Me	Me					1
4					OH		1
5					OMe		1
6				OMe	OMe		1
7				OMe	OMe	OMe	1
8	Me			OMe	OMe	OMe	1
9							2
10			Me				1
11	Me		Me				1

and amphetamine (**10**), and their N-methylated derivatives possess a single alkylamino side chain on the benzene ring, and are expected to have first and second IP's involving orbitals essentially identical with the Ph_s and Ph_a orbitals of toluene.

In phenethylamine, the Ph_s and Ph_a orbitals are not resolved, since the broad featureless band due to the amino lone pair (n_N) orbital appears in the same region of the spectrum (cf. $MeNH_2$, which has a vertical IP of 9.66 eV).[15] In γ-phenylpropylamine and amphetamine, the Ph_a IP's are partially resolved and appear at 9.22 and 9.26 eV, respectively. The Ph_s IP's of these molecules are around 8.9 eV, but the superposition of the n_N orbitals obscures these bands to some extent.

Identification of the location of the n_N IP, as well as the location of the Ph_s and Ph_a bands, is facilitated by N-methylation. The expected decrease in the n_N IP (cf. $MeNH_2$ (9.66 eV), Me_2NH (8.94 eV), Me_3N (8.50 eV))[15] is observed upon N-methylation of the phenethylamines. The n_N band of *N*-methylphenethylamine lies near 8.7 eV, and emerges as a well-resolved band at 8.35 eV in *N,N*-dimethylphenethylamine. Similarly, the IP's of the secondary amino group in methamphetamine and *N*-methylmescaline appear at 8.60 and 8.69 eV, respectively. Since the secondary amines are expected to have IP's 0.6–0.8 eV lower than those of the primary amines, the n_N orbitals in the latter must lie at 9.2–9.5 eV, that is, overlapping the Ph_s and Ph_a bands of these molecules.

Substitution of phenethylamine at the 4 position will affect

Table I. IP's of Phenethylamines[a]

β-Phenethylamine (**1**)	8.99 ± 0.20 (sh), 9.35 ± 0.16
N-Methylphenethylamine (**2**)	8.66 ± 0.20 (sh), 9.08 ± 0.16, 9.32 ± 0.20 (sh)
N,N-Dimethylphenethylamine (**3**)	8.35 ± 0.14, 8.95 ± 0.16, 9.27 ± 0.20 (sh)
4-Hydroxyphenethylamine (**4**)	8.41 ± 0.12, 9.35 ± 0.12
4-Methoxyphenethylamine (**5**)	8.16 ± 0.08, 9.19 ± 0.10
3,4-Dimethoxyphenethylamine (**6**)	8.03 ± 0.16, 8.86 ± 0.16, 9.30 ± 0.20, 9.99 ± 0.12, 10.86 ± 0.20 (sh), 11.37 ± 0.20 (sh)
Mescaline (**7**)	8.18 ± 0.24, 9.29 ± 0.20 (sh), 9.79 ± 0.16, 10.24 ± 0.10
N-Methylmescaline (**8**)	8.44 ± 0.40, 9.29 ± 0.20, 9.79 ± 0.16, 10.24 ± 0.10
γ-Phenylpropylamine (**9**)	8.89 ± 0.12, 9.22 ± 0.08
Amphetamine (**10**)	8.91 ± 0.14, 9.26 ± 0.10
Methamphetamine (**11**)	8.60 ± 0.20, 9.05 ± 0.10, 9.29 ± 0.20

[a] Error limits are the peak half-width at 90% height or 0.05 eV, whichever is greater.

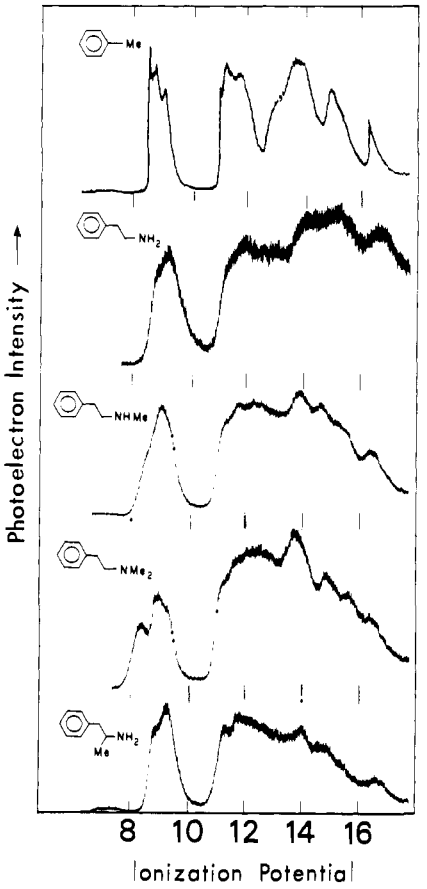


Figure 2. Photoelectron spectra of toluene, phenethylamine, *N*-methylphenethylamine, *N,N*-dimethylphenethylamine, and amphetamine.

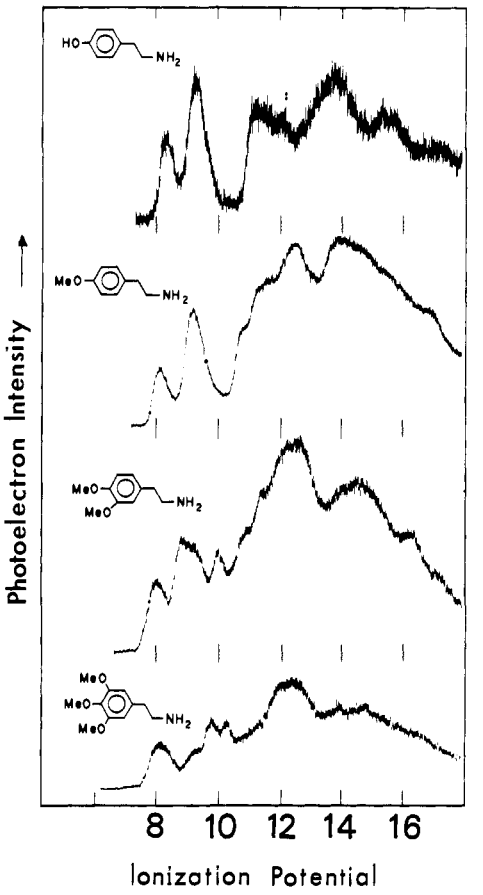


Figure 3. Photoelectron spectra of 4-hydroxy-, 4-methoxy-, 3,4-dimethoxy-, and 3,4,5-trimethoxyphenethylamines (mescaline).

the Ph_s IP's to a large extent and those of Ph_a to a small, or negligible, extent. The Ph_s bands of 4-hydroxyphenethylamine (8.41 eV) and 4-methoxyphenethylamine (8.16 eV) are shifted markedly to lower IP's relative to the Ph_s band of phenethylamine (9.0 eV). By comparison, phenol has an IP of 8.73 eV, 0.52 eV lower than that of benzene, while anisole has an IP of 8.39 eV, 0.68 eV less than that of benzene.[16] Thus, 4-hydroxy and 4-methoxy groups affect Ph_s IP's of the phenethylamines to nearly the same extent as they affect those of benzene.

The Ph_a IP's of these compounds are not clearly resolved due to the overlapping n_N band. Thus, the maxima at 9.35 and 9.19 eV are not necessarily the vertical IP's of Ph_a. In any case, these IP's are expected to be very similar to those of the parent molecules, as they are in phenol (9.40 eV) and anisole (9.22 eV).[16]

Addition of a third substituent to these molecules will destroy the C_{2v} symmetry, and the first two IP's will no longer be identifiable as ionizations from Ph_s and Ph_a orbitals. For example, on going from 4-methoxyphenethylamine to 3,4-dimethoxyphenethylamine, considerable mixing of the Ph_s and Ph_a orbitals occurs as shown in Figure 4 by CNDO/2 calculations. (Calculations on this series will be discussed in more detail later.) While the HOMO remains primarily Ph_s in character, admixture with Ph_a enhances the effect of the second methoxy group on HOMO. The IP's for the first two bands of 3,4-dimethoxyphenethylamine fall at 8.03 and 8.86 eV, approximately 0.2 to 0.3 eV lower than those for 4-methoxyphenethylamine, and in good agreement with the IP's of 3,4-dimethoxytoluene at 7.95 and 8.71 eV.

From the coefficients of the CNDO/2 orbitals of the 4-methoxy (**5**) and 3,4-dimethoxy (**6**) compounds, it may be estimated[17] that the HOMO has nine times as much Ph_s as Ph_a character from **5**, while the SHOMO (second highest occupied molecular orbital) of **6** has three times as much Ph_a as Ph_s character from **5** (Figure 4).

The four substituents on the ring in mescaline restore the

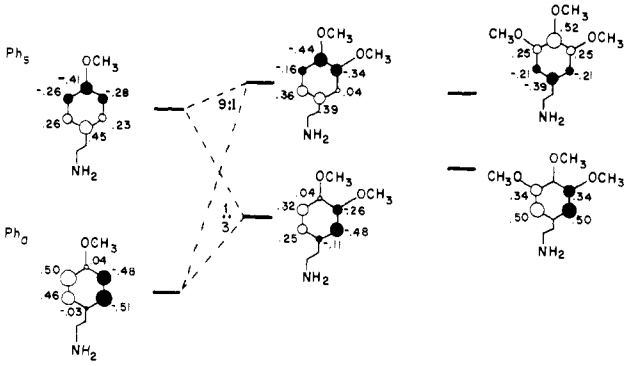


Figure 4. The HOMO and SHOMO of 4-methoxyphenethylamine, 3,4-dimethoxyphenethylamine, and mescaline (CNDO/2).

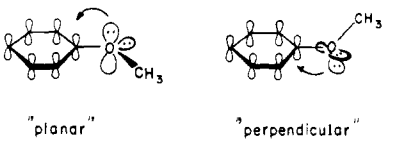


Figure 5. "Planar" and "perpendicular" conformations of anisole.

C_{2v} symmetry of this molecule, so that once again IP's can be discussed in terms of Ph_s and Ph_a orbitals. The addition of two methoxy groups at the 3 and 5 positions of 4-methoxyphenethylamine to give mescaline causes the Ph_a band to merge with the Ph_s, resulting in one broad peak at 8.18 eV. The added methoxy groups exert a greater effect on the Ph_a band than on the Ph_s band: the Ph_a band has been shifted to lower IP's by 0.9 to 1.1 eV, while the Ph_s band has been shifted by ±0.2 eV, if at all.

In spite of the presence of three donor methoxyl groups in mescaline and only two in 3,4-dimethoxyphenethylamine, the latter has the same IP as, or a somewhat lower IP than mescaline! In fact, 4-methoxyphenethylamine and mescaline have almost identical lowest IP's. The origin of this anomaly must lie in the inability of three contiguous methoxy groups to all be coplanar with the phenyl group.

Calculations indicate that the preferred conformation of anisole and other methoxyaromatics has the methyl carbon in the plane of the aryloxy group ("planar" conformation in Figure 5),[18] and NMR data confirm this preference.[19] This conformation has the oxygen 2p lone pair in ideal location for electron donation by conjugation with the benzene π system.[20] The higher energy "perpendicular" conformation will have much poorer electron donation from the oxygen sp^2 lone pair. In fact, in this conformation, the methoxyl may act as a net inductive electron withdrawer.

Schweig and Thon have provided dramatic evidence for the difference between aromatic ionization potential lowering by "p-type" and "sp^2-type" lone pairs.[21] Thioanisole exists as two rotameric forms in the gas phase. Temperature-dependent photoelectron spectroscopy reveals that the lower energy form, which corresponds to the "planar" conformation, has a vertical IP of 8.02 eV, while the higher energy "perpendicular" conformation has a vertical IP of 8.55 eV.[21] While similar evidence on anisole is unavailable, the photoelectron spectra of certain bicyclic enol ethers show that an ether oxygen attached to a double bond raises the IP of the π orbital of the alkene, if the oxygen "p-type" lone pair is prevented from conjugating with the π orbital.[22]

In 3,4-dimethoxyphenethylamine, both methoxyls may be "planar", while the 4-methoxyl group cannot be planar in mescaline. Recent neutron diffraction studies on a related compound, trimethoprim, indicate that the central methoxyl is rotated 101° out of plane; that is, the 4-methoxyl is only 11° away from the "perpendicular" conformation.[23] The relatively high first IP of mescaline can be attributed to the relatively small effect of the 3- and 5-methoxyls on the Ph_s IP and the small lowering, or even IP-raising effect of a perpendicular 4-methoxyl group.

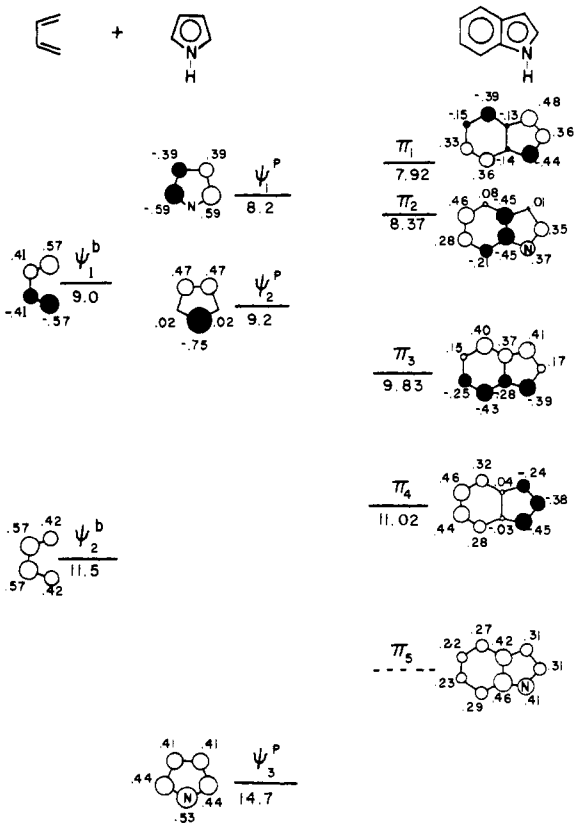


Figure 6. The π MO's of butadiene, pyrrole, and indole.

Table II. IP's of the Ph_s and Ph_a Orbitals of Phenethylamines and Toluenes

Substituent	Phenethylamines		Toluenes	
	Ph_s	Ph_a	Ph_s	Ph_a
Parent	9.0	9.2	8.72[a]	9.24[a]
Amphetamine	8.9	9.2	8.72[a]	9.24[a]
4-Hydroxy	8.4	9.2	8.38[b]	9.25[b]
4-Methoxy	8.2	9.2	8.18[b]	9.11[b]
3,4-Dimethoxy	8.0	8.9	7.95[c]	8.71[c]
3,4,5-Trimethoxy	8.1–8.3		~8.13[d]	~8.13[d]

[a] Reference 14. The Ph_s band of toluene has a sharp peak at 8.72 eV with a broad peak near 8.9 eV. In the phenethylamines this sharp vibrational structure is lost due to the relative conformational freedom of the side chain. [b] Reference 12. [c] This work. Additional IP's at 9.91, 10.72, and 11.36 eV. [d] This work. Additional IP at 10.21 eV.

Similar effects are noted in simpler analogues. Thus, 3,4,5-trimethoxytoluene has an IP_1 nearly identical with that of 4-methoxytoluene (Table II). Dewar and co-workers reported the IP's of a number of alkoxy and 1,3-dimethyl-2-alkoxybenzenes.[21b] In each case, the latter have higher IP's than the former (e.g., anisole IP = 8.46 eV; 2,6-dimethylanisole IP = 8.53 eV), in spite of the expected electron release by the methyl groups.

As can be seen from the data in Table II, a good correlation exists between the lower IP's of the substituted toluenes and their corresponding phenethylamines. The absence of anomalies within this series indicates that the amino group of

Table III. IP's of Tryptamines[a]

	π_1	π_2	π_3	π_4	n_N
Indole[b]	7.92 ± 0.05	8.37 ± 0.06	9.83 ± 0.05		
Tryptamine (**12**)	7.69 ± 0.08	8.25 ± 0.08	9.63 ± 0.08		9.25 ± 0.16
N-Methyltryptamine (**13**)	7.60 ± 0.08	8.25 ± 0.08	9.56 ± 0.06		8.87 ± 0.16
N,N-Dimethyltryptamine (**14**)[c]	7.57 ± 0.05	8.22 ± 0.06	9.54 ± 0.06		~8
Gramine (**15**)	7.69 ± 0.16	8.19 ± 0.10	9.59 ± 0.06		~8
5-Methyltryptamine (**16**)	7.64 ± 0.05	8.03 ± 0.08	9.54 ± 0.08		9.18 ± 0.16
5-Methoxytryptamine (**17**)	7.68 ± 0.12	7.79 ± 0.12	9.66 ± 0.10	10.22 ± 0.08	9.19 ± 0.20
N,N-Dimethyl-5-methoxytryptamine (**18**)	7.61 ± 0.14	7.8 ± 0.2	9.50 ± 0.10	10.08 ± 0.06	8.18 ± 0.20

[a] See footnote to Table I. [b] IP of band is given as the average of the most intense vibrational peaks: π_1 7.75, 7.92, 8.08; π_2 8.37; π_3 9.08, 9.86 eV. [c] π_1 7.50, 7.64 eV.

phenethylamines does not interact in any specific through-space fashion with the phenyl ring in the gas phase.

Tryptamine Molecular Orbitals. The changes in MO energies in tryptamines upon substitution can be predicted using a simple PMO approach based on indole. Indole may be considered formally as either a 1,3-butadiene unit fused to a pyrrole ring at the 4 and 5 ring carbon atoms, or as an enamine moiety fused to a benzene ring. For convenience, we will use the former description. The π-MO descriptions and photoelectron IP's of butadiene,[24] pyrrole,[25] and indole[26] are given in Figure 6. The π orbitals of butadiene interact with those of pyrrole to give the indole π orbitals. The extent of interaction of butadiene MO's with pyrrole MO's is determined by the magnitude of the coefficients, the local symmetry, and the relative energies of the molecular orbitals. MO's which are close in energy, have the same symmetry, and have large coefficients at the site of fusion will interact the most. The symmetry of the butadiene and pyrrole components is not preserved in the product indole, however, so that all of the orbitals can interact to some extent. A comparison of the experimental IP's and calculated (CNDO/S) coefficients of butadiene, pyrrole, and indole reveals the origin of the various indole orbitals in terms of the MO's of the constituent parts.[17]

The HOMO of indole resembles ψ_1^b (40%), mixed in an antibonding fashion with both ψ_1^p (28%) and ψ_2^p (25%). The antibonding interaction is determined by the position of the larger ψ_1^p and ψ_2^p coefficients; that is, C-2 in ψ_1^p and C-3 in ψ_2^p. The indole HOMO also has a small admixture of ψ_2^b (1%). The HOMO has large coefficients at the pyrrole moiety and at positions 4, 6, and 7, and a small coefficient at 5. The resemblance of the HOMO to the antisymmetric (a_2 in C_{2v}) phenyl orbital (with 5 and 8 the C_2 axis) is striking.

The corresponding bonding combination of ψ_1^b (41%) with ψ_1^p (8%) and ψ_2^p (43%) is assigned to the third orbital, which gives rise to the IP at 9.83 eV in indole. This and the first IP arise from an orbital which has smaller coefficients at positions 5 and 6 than at 4 and 7, because of the origin of these orbitals in ψ_1^b. The orbital also resembles the a_2 orbital of C_{2v} aromatics, with 5 and 8 containing the C_2 axis.

The second IP arises from an orbital, π_2, which is composed of the antibonding combination of ψ_2^b (13%) with ψ_1^p (42%) and ψ_2^p (23%). Because of the origin of the orbital, it is more heavily localized on the pyrrole than the benzene moiety, and has larger coefficients at positions 5 and 6 than at 4 and 7. The resemblance here is to the b_1 orbital of aniline or other monosubstituted benzenes of C_{2v} symmetry. The lower energy π orbitals of indole consist mainly of combinations of ψ_2^b and ψ_3^p.

Palmer and Kennedy have carried out ab initio calculations on indole, and their discussion of the orbital shapes is in qualitative agreement with Figure 6. The similarity of the indole MO's to those of naphthalene was also noted by these authors.[27]

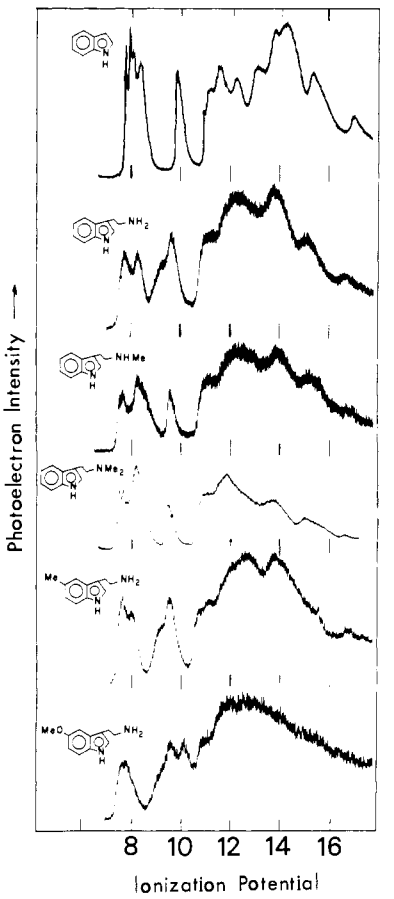


Figure 7. Photoelectron spectra of indole, tryptamine, *N*-methyltryptamine, *N,N*-dimethyltryptamine, 5-methyltryptamine, and 5-methoxytryptamine.

Photoelectron Spectra of Tryptamines. The photoelectron spectra of indole, gramine, and the tryptamines studied here are given in Figure 7, and the vertical IP's are listed in Table III.

The spectrum of indole consists of several bands at low IP's accompanied by vibrational splittings: π_1 7.92 (1400 cm^{-1}), π_2 8.37, and π_3 9.83 eV (500 cm^{-1}). This is in good agreement with that of Güsten and co-workers[26] for indole: π_1 7.91 (1370 and 640 cm^{-1}), π_2 8.37, and π_3 9.78 eV (480 and 1370 cm^{-1}). For comparison, pyrrole has bands at 8.2 (1020 and 1370 cm^{-1}) and 9.2 eV,[25] and butadiene at 9.06 eV (520, 1200, and 1500 cm^{-1}).[24]

Electron-donating substituents on the indole ring will increase the energies (decrease the IP's) most of the indole molecular orbitals with the largest coefficients at the site of substitution. On the basis of the coefficients in Figure 6, substitution of an alkyl or the ethylamine moiety at the 3 position of

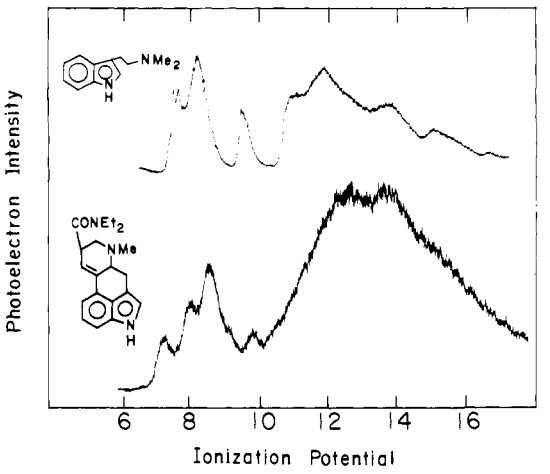
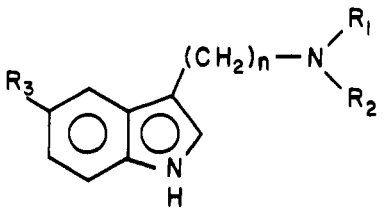


Figure 8. Photoelectron spectra of dimethyltryptamine and lysergic acid diethylamide (LSD).

the indole ring to give tryptamine is expected to raise the π_1 and π_3 molecular orbital energies substantially and leave π_2 essentially unchanged, to first order. As shown in the spectra and Table III, π_1 and π_3 are shifted to lower ionization potentials by 0.23 and 0.20 eV, respectively, on going from indole to tryptamine, while π_2 is shifted 0.12 eV to lower ionization potential and π_4 remains under the σ envelope. Similarly, a methyl substituent at the 3 position of indole lowers the ionization potentials of π_1, π_2, and π_3 by approximately 0.2–0.3 eV.[26,28]

In the tryptamine spectrum, the broad band centered at 9.25 eV is attributed to ionization from the nitrogen lone pair of the ethylamine substituent. As with the phenethylamines, methylation of the amino group shifts the n_N peak to lower IP's, but does not affect the IP's of the aromatic moiety. The n_N IP is lowered from 9.25 eV in tryptamine to 8.9 eV in *N*-methyltryptamine, and finally to around 8 eV under the π_1 and π_2 peaks of *N,N*-dimethyltryptamine.

The photoelectron spectrum of gramine, **15**, is expectedly similar to that of *N,N*-dimethyltryptamine. Here, as with *N,N*-dimethyltryptamine, the n_N band is obscured by the π_1 and π_2 bands of the indole ring.



	R_1	R_2	R_3	*n*
12				2
13	Me			2
14	Me	Me		2
15	Me	Me		1
16			Me	2
17			MeO	2
18	Me	Me	MeO	2

Substitution of an electron donor, such as methyl or methoxyl, at the 5 position of tryptamine will raise π_2 and π_4 considerably in energy; π_1 and π_3 will also be shifted, but by a much smaller amount due to the small coefficients at C-5 in these orbitals (Figure 6). The vertical ionization potentials listed in Table III show that the π_2 band has been shifted to 8.03 eV, 0.22 eV to lower IP for 5-methyltryptamine and to 7.79 eV, 0.46 eV to lower IP, for 5-methoxytryptamine. Additionally, in 5-methoxytryptamine, π_4 is now separated from the σ envelope and lies at 10.22 eV. The greater shift for the

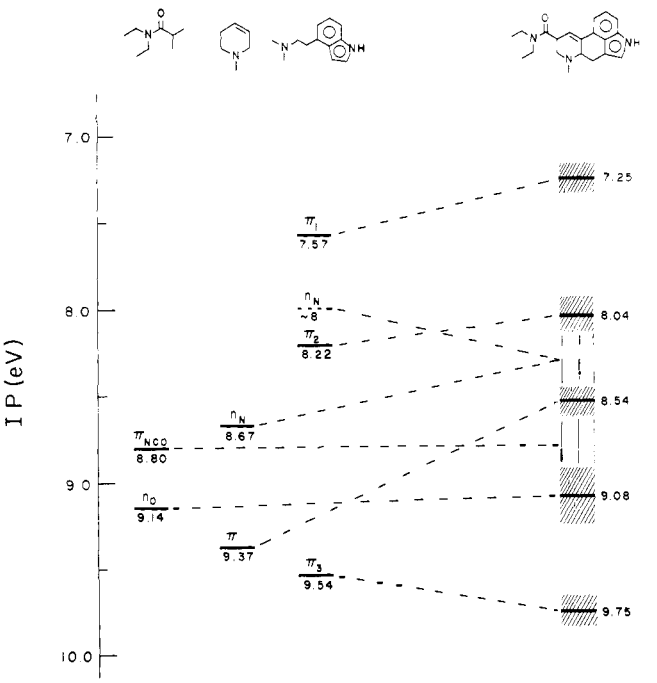
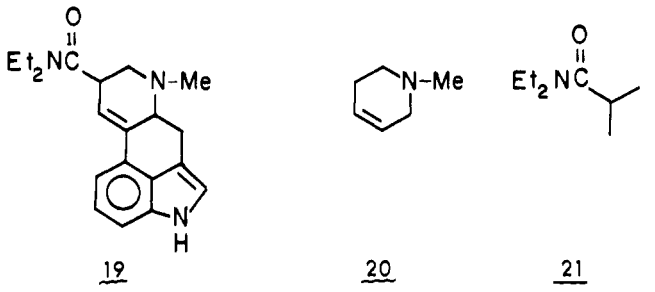


Figure 9. Ionization potentials of LSD and model compounds, dimethyltryptamine, 1,2,5,6-tetrahydropyridine, and diethylisobutyramide.

methoxyl-substituted tryptamine relative to the methyl substituted is consistent with the greater conjugative effect of a methoxyl group relative to a methyl group. Similar shifts are also observed for substituted benzenes: the first IP is lowered by 0.86 eV for anisole (8.9 eV)[16] and by 0.53 eV for toluene (8.72 eV).[14]

Photoelectron Spectrum of Lysergic Acid Diethylamide (LSD) (19).[44] LSD is the most potent hallucinogen[7] in terms



19 20 21

of human dose, so that it is of special interest in relationship to the other (less active) tryptamines studied here.

The photoelectron spectrum of LSD is shown in Figure 8, along with that of the simpler analogue, *N,N*-dimethyltryptamine (DMT). To facilitate assignment of the various bands to ionizations arising from orbitals on the indole, tertiary amine, or amide moieties, the vertical ionization potentials observed for LSD are compared (Figure 9) with those of models for the indole (*N,N*-dimethyltryptamine), tertiary amine and alkene (*N*-methyl-1,2,5,6-tetrahydropyridine (**20**)), and amide (*N,N*-diethylisobutyramide (**21**)) moieties present in LSD.

As discussed earlier, the lowest three π ionization potentials of *N,N*-dimethyltryptamine occur at 7.57, 8.22, and 9.54 eV, while the tertiary amine lone pair gives rise to an unresolved ionization near 8 eV. An isolated trisubstituted alkene such as the 9,10-double bond in LSD would have an ionization potential of less than 9.37 eV, the value of the π IP of 1,2,5,6-tetrahydro-*N*-methylpyridine (**20**).[29] Conjugation of this π orbital with the π orbitals of the indole moiety of tryptamine will be appreciable, since these systems are mutually twisted

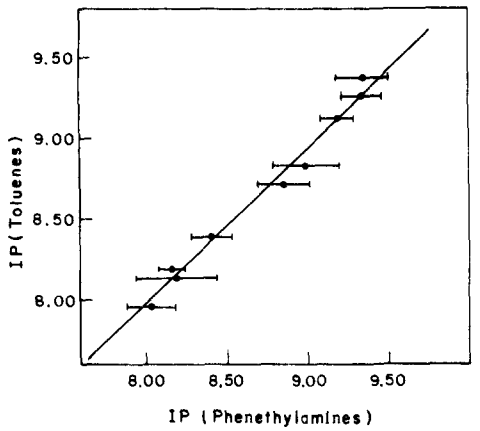


Figure 10. Plot of first and second IP's of substituted toluenes vs. those of the corresponding phenethylamines.

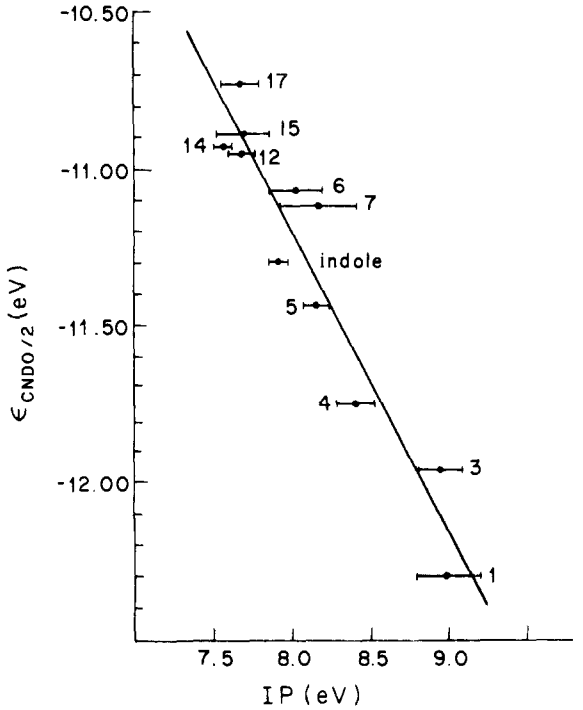


Figure 11. Plot of CNDO/2 HOMO energies vs. vertical IP's of some phenethylamines and tryptamines.

by only 11° in LSD. This conjugation will have a relatively large effect on the lowest two DMT-like ionization potentials, which arise from orbitals, π_1 and π_2, which are higher in energy than the trisubstituted alkene orbital. Thus, mixing of π_1 and π_2 with the alkene orbital will cause a destabilization of the two highest indole orbitals and a stabilization of the alkene orbital. The mixing of the alkene π orbital with the third π orbital of the indole moiety will destabilize the alkene orbital and stabilize π_3. As shown in Figure 9, these considerations lead to assignment of the 7.25 ± 0.10, 8.04 ± 0.12, 8.54 ± 0.09, and 9.75 ± 0.10 eV ionization potentials to those arising from the orbitals of the 4-vinylindole π system. Three other low-energy ionizations are expected in the 7–9 eV region of the spectrum. The tertiary amine lone pair ionization will be similar to that in the tetrahydropyridine model (8.67 eV).[29] This ionization must be in the intense region around 8.4 eV, which contains several ionization bands. *N,N*-Dimethylisobutyramide, studied here, has carbonyl-nitrogen (π_{NCO}) and oxygen (n_O) ionization potentials of 8.80 and 9.14 eV, respectively. The former type is undoubtedly in the unresolved 8.5–9.0-eV region of the LSD spectrum, while the latter is assigned to the 9.08 ± 0.20-eV shoulder in the LSD spectrum.

The lower π ionization potential of LSD (7.25 eV) is significantly lower than that of *N,N*-dimethyltryptamine (7.57 eV) and other substituted tryptamines studied here. Nevertheless, the first ionization potential of LSD is not abnormally low as compared to other good electron donors such as phenothiazines and related neuroleptics which we have studied.

Discussion

Substituent Effects on IP's. Substituents on the aromatic rings of phenethylamines have a normal influence on IP's. That is, the donor ability of the group and the site of substitution (and coefficients at that site in the MO of interest) determine the extent of change in aromatic IP's in a normal fashion. Furthermore, although side-chain substituents cause substantial changes in the amine lone pair IP, these groups influence the aromatic IP's to a negligible extent. Thus, data on substituted benzenes[14,16,30] will be of great value in the prediction of phenethylamine IP's. In fact, as we have pointed out before, the substituted toluenes are ideal models for substituted phenethylamines (Table II). Figure 10 shows this graphically. Substituted 3-methylindoles (skatoles) would undoubtedly serve as useful models for substituted tryptamines, also. However, the availability and convenience of handling skatole, an odoriferous component of human feces, is somewhat offset by its most apparent physical property!

One effect which prevents simple additivity of substituent effects in highly substituted derivatives is the impossibility of having all groups, such as methoxyls, simultaneously in a conformation which will lead to maximum IP lowering. Thus, simply adding more donor substituents to the aromatic ring does not necessarily lead to a lowering of the IP of the molecule.

Correlations between Experimental IP's and Calculated Orbital Energies. A number of workers have concluded that the donor abilities of phenethylamines and tryptamines determine their activities on the basis of correlations between HOMO energies and drug activities. For this reason, it is of some importance to determine whether there is any correlation between experimental IP's and those calculated from semiempirical calculations using Koopmans' theorem.

Although CNDO/2 calculations do not reliably reproduce absolute energies, they are capable of predicting trends within a series of closely related molecules. As shown in Figure 11, there is a reasonable correlation between calculated CNDO/2 HOMO energies[31] and the first IP's of the phenethylamines and tryptamines. Although the calculated CNDO/2 HOMO energies for the tryptamines varied in a normal fashion with changes in substitution on the aromatic ring, the experimental IP's of these compounds are nearly constant. Thus, even though the errors in experimental IP's are large (conservatively estimated by the error bars in Figure 11), the CNDO/2 calculations fail to quantitatively reproduce the experimental IP's, probably due to assumptions about geometries made in the calculations.

Theoretical Relationships between Ionization Potentials and Reactivity with Electrophiles or Charge Transfer Donor Ability. As shown in the next section for these compounds, the relationship between electron-donor ability and ionization potentials may be something more complicated than just a linear relationship with the first IP of a molecule. For that reason, a brief discussion of the theoretical connection between ionization potentials and reactivity or charge transfer complexation ability is in order here.

The energy of interaction of an electron donor with an electrophile or an electron acceptor can be conveniently formulated in terms of the perturbation formalism applied to electron donor-acceptor complexes.[10] It should be emphasized that a theory of this type may be applied to either weak com-

plexes or to transition states of reactions,[32] so that correspondence between increasing reactivity (or activity) and decreasing ionization potential does not necessarily implicate the specific mechanism involved in reactivity (or activity) other than to show that the reagent or complexing agent is electrophilic, or electron accepting, and that the electron-donating ability dictates, in large part, the reactivity (or activity) of the series of molecules. A more extensive discussion of this point may be found in ref 32.

In terms of ionization potentials of a donor molecule and electron affinities (EA's) of an acceptor, the stabilization (ΔE) of a molecular complex (or transition state) arising from charge transfer is approximately:

$$\Delta E \cong -\sum_{a,i} \frac{H_{a,i}^2}{IP_a - EA_i - Q}$$

where the sum runs over all the occupied orbitals, a, of the donor and the vacant orbitals, i, of the acceptor. That is, for each filled orbital of the donor and vacant orbital of the acceptor, there will be a charge-transfer interaction which depends directly on the square of the resonance integral between orbitals a and i, $H_{a,i}$, and inversely upon the difference between the energies of the interacting orbitals.[33] The quantity, Q, represents the decrease in energy required to transfer an electron from a to i as the molecules are brought from infinite separation ($Q = 0$) to bonding distance ($Q \approx 4$ eV); Q is approximately constant for similar complexes.[10,32] The resonance integral, $H_{a,i}$, depends approximately upon the overlap between a and i in the geometry of the molecular complex.

It is clear from this equation that all filled orbitals of the donor and vacant orbitals of the acceptor are important in determining the stabilization of the molecular complex. However, the HOMO of the donor and LUMO of the acceptor contribute the most to complex stabilization, since they are closest in energy. This is the basis of the well-known "frontier orbital" approximation.[32]

However, for molecules with a number of closely spaced high-lying orbitals, the frontier orbitals may not contribute significantly more to complex stabilization than other orbitals. To develop this idea somewhat more quantitatively, we assume, without loss of generality, that a model acceptor has a single low-lying vacant orbital which gives rise to an EA of 1 eV. Using the "typical" value of Q of 4 eV, the perturbation expression becomes (in eV):

$$\Delta E = -\sum_{a,i} [H_{a,i}^2/(IP_a - 5)]$$

Assuming that $H_{a,i}$ is constant for interaction of each occupied orbital of the donor with the vacant acceptor orbital (which will not generally be the case),[42] several example ΔE's have been calculated for molecules discussed here.

For phenethylamine, which has IP's of approximately 9.0, 9.4, and 11.0 eV, the quantity $[IP - 5]^{-1}$ is 0.25, 0.23, and 0.17, respectively. Clearly, if all three orbitals overlap equally well with the acceptor orbital, all three interactions would contribute similarly to complex stabilization. The HOMO and SHOMO contribute 74% of the stabilization energy. For indole, with IP's of 7.9, 8.4, 9.8, and 11.0 eV, the quantity $[IP - 5]^{-1}$ is 0.34, 0.29, 0.21, and 0.17, respectively. The top two MO's contribute 62% of the stabilization energy. Unless lack of overlap excludes interactions of some orbitals, or unless some orbitals do not change in energy upon substitution, all relatively high-lying orbitals should be considered in attempted correlations between IP's and complex stabilization.

So far, only the charge-transfer, or delocalization, contribution to stabilization has been discussed. However, it has been amply demonstrated that dispersion energy contributes significantly to stabilization of molecular complexes.[34,35] Haselbach and co-workers simplified the London equation,

$$E_{dispersion} = \frac{3IP_D IP_A}{2(IP_D + IP_A)} \cdot \frac{\alpha_D \alpha_A}{d_{AD}^6}$$

to the following form:[35]

$$E_{dispersion} \cong KIP_D\alpha_D/(IP_D + IP_A)$$

The simplification assumes a constant acceptor and a constant distance, d_{AD}, between the donor and acceptor. The polarizability of the acceptor, α_A, is a constant and is absorbed into the catch-all constant, K. If it is assumed that the polarizability of a series of donors is a constant (or is linearly related to IP_D), then further simplification can be made:

$$1/E_{dispersion} = K' + K''/IP_D$$

This is a very crude equation, since it is an approximation to an already approximate equation derived for the interaction of atoms! If the stability of a charge-transfer complex depends on dispersion energy, a linear relationship might be expected between the inverse of the stability constant and the inverse of the ionization potential of the donor.

Morokuma has recently calculated the dispersion energy contribution to the stabilization of a model charge-transfer complex.[45] The second-order sum-of-state perturbation approximation was used in which interactions of various singly-excited configurations of the two molecules are calculated. Put relatively simply:

$$E_{dispersion} = \frac{H_{D^*-A^{*2}}}{E_{D^*} + E_{A^*} - E_0}$$

where $H_{D^*-A^*}$ is the interaction between singly-excited configurations, D* and A*, on the donor and acceptor, and E_{D^*} and E_{A^*} are the energies of these configurations, respectively. E_0 is the energy of the ground configuration. If we make the following gross, but qualitatively justifiable assumptions: (1) the largest term involves the HOMO's and LUMO's of the two molecules (the lowest excited states of each), (2) donors affect the HOMO's more than the LUMO's, and (3) the electron repulsion and orbital interaction terms figuring into the calculation of excited state energies and the numerator of the above expression remain approximately constant, then this expression simplifies to

$$E_{dispersion} = \frac{K}{IP_D + K'}$$

Either method of dispersion energy calculation indicates that there should be a relationship between IP_D and stabilization energy. Although the final functional forms obtained by making gross assumptions are different, over the range of IP's studied, approximately linear plots can be obtained by plotting stabilization energy vs. IP_D or IP_D^{-1}.

Finally, on a more empirical level, Figure 12 shows that for relatively well-behaved solution complexes of aromatic hydrocarbons with TCNE, the enthalpy of formation, ΔH_{app}, measured by Haselbach and co-workers,[35] correlates better with the average of the first and second IP's, $IP_{av} = [IP_1 + IP_2]/2$, than with the first IP's of the aromatic hydrocarbons. The IP_{av} better represents donor ability, particularly for molecules like mesitylene (**26**), which has two degenerate low-energy IP's, and is overall a better donor than *o*- or *p*-xylene, each of which has an IP_1 equal to or lower than that of mesitylene, but a considerably higher IP_2.

The least-squares correlation for IP_1 is:

$$-\Delta H_{app} = -3.07IP_1 + 29.5$$

which has a correlation coefficient (r) of 0.925. The correlation for IP_{av} is

$$-\Delta H_{app} = -3.37IP_{av} + 32.4$$

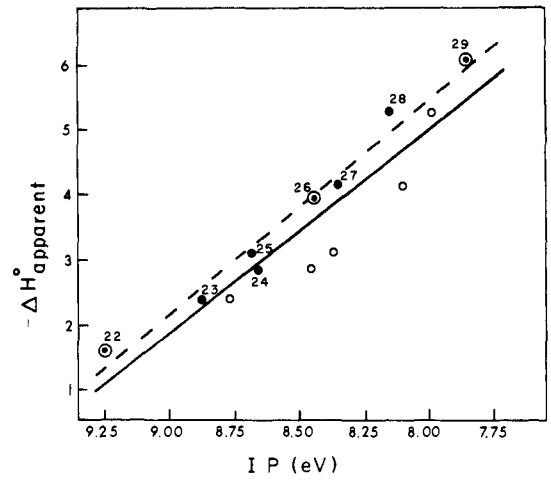


Figure 12. Plots of apparent enthalpies of formation of aromatic hydrocarbon–TCNE complexes vs. IP_1 (○) or $IP_{av} = (IP_1 + IP_2)/2$ (●) of the aromatic hydrocarbon: **22**, benzene; **23**, toluene; **24**, *o*-xylene; **25**, *p*-xylene; **26**, mesitylene; **27**, 1,2,4,5-tetramethylbenzene; **28**, pentamethylbenzene; **29**, hexamethylbenzene. Solid line is for IP_1; broken line is for IP_{av}.

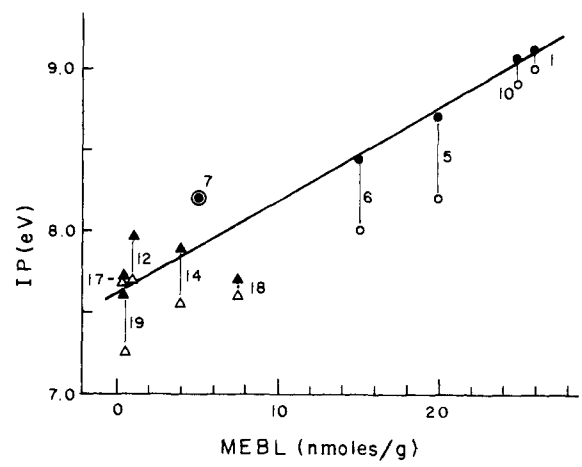


Figure 13. Plot of the first π ionization potential and the average of the first two π ionization potentials (IP's) of hallucinogens and related compounds vs. the minimum effective brain level (*MEBL*) to alter rat behavior in a conditioned avoidance response. (**19** = LSD; **18** = 5-methoxydimethyltryptamine; **17** = 5-methoxytryptamine; **14**, = dimethyltryptamine; **7** = mescaline; **6** = 3,4-dimethoxyphenethylamine; **5** = 4-methoxyphenethylamine; **10** = amphetamine; **1** = phenethylamine; **12** = tryptamine after MAO inhibition. Tryptamine derivatives: IP_1 = △ and IP_{av} = ▲. Phenethylamine derivatives: IP_1 = ○ and IP_{av} = ●.) The line is for IP_{av}.

with a correlation coefficient of 0.987. The correlation lines are shown in Figure 12.

Correlations between Ionization Potentials and Behavioral Activity. While we defer a complete discussion of this subject until a more extensive series of compounds has been studied, certain general trends are worth noting.

Snyder and Merril[3a] and Green and Kang[3b] have found correlations between calculated HOMO energies and hallucinogenic activity for phenethylamines and tryptamines. Both groups based their correlations on hallucinogenic activity in humans as determined by Shulgin in terms of "effective" dosage of a given drug with respect to that of mescaline.[36] The vertical IP's of the first band of the phenethylamines (Table III) correlate fairly well ($r > 0.9$) with the corresponding HOMO energies calculated by Snyder and Merril with a simple Hückel method,[3a] by Green and Kang with INDO,[3b] and in this work with CNDO/2 (Figure 11). We find, however, no significant correlation between the first IP of **1**, **5**, **6**, and **7**, measured here, and the corresponding effective human dosage.[36] This is due, primarily, to the small difference between the IP's of **6** and **7** as compared to the large differences in activity, mescaline (**7**) having far greater activity than 3,4-dimethoxyphenethylamine (**6**).

Barfknecht, Nichols, and Dunn have found evidence for a correlation between hallucinogenic activity in humans and lipophilicity as determined by 1-octanol-water partition coefficients for a variety of phenethylamines and amphetamines.[37] However, their data indicated that lipophilicity alone was not sufficient to explain hallucinogenic activity and that electronic factors of substituents must be taken into account.

In order to separate inherent activity of drugs in influencing behavior from other effects such as propensity for the drug to cross the blood-brain barrier, Vogel and Evans have measured the minimal effective brain level, MEBL (nmol/g), required for the drug to interfere with the conditioned avoidance response of rats in the shuttle box.[38] In Figure 13, the data of Vogel and Evans are plotted against both the lowest vertical π IP measured here, and against the average of the first and second vertical π IP's. The first IP's correlate more poorly with activity than the average IP's, but the average IP's correlate well with activity only for the phenethylamines. The least-squares correlation for IP_1 is

$$MEBL = 15.5IP_1 - 114$$

which has a correlation coefficient (r) of 0.89. The correlation for IP_{av} is

$$MEBL = 17.2IP_{av} - 132$$

with a correlation coefficient of 0.95. Because electron-donating substituents lower IP's of molecular orbitals with substantial coefficients at the site of substitution, large shifts to lower IP's are observed for both the first and second IP's from the aromatic moiety of the phenethylamines and tryptamines. Although changes in the first IP can account for increased activity in the series phenethylamine, 4-methoxyphenethylamine, and 3,4-dimethoxyphenethylamine, the greater activity of mescaline over 3,4-dimethoxyphenethylamine and of 5-methoxytryptamine over tryptamine cannot be accounted for by changes in their first IP's alone. In both cases, the first IP is not lowered to any appreciable extent, while the second IP is lowered dramatically.

In the whole series, the third and higher IP's do not change dramatically, as judged by the similarity in the positions of onsets and shapes of the envelope of bands beginning at about 10.5 eV. The only exceptions to this are mescaline, and to a lesser extent 3,4-dimethoxyphenethylamine. In both these compounds, one or more IP's, which may involve the aromatic ring, appear at less than 10.5 eV. Perhaps the deviation of mescaline from the least-squares line in Figure 13 can be attributed to our neglect of IP's other than IP_1 and IP_2 in IP_{av}. The correlation of IP_{av} with phenethylamine activities resembles the aromatic-TCNE charge-transfer complexes discussed earlier, where IP_{av} is a better indicator of complex stability than IP_1. Similarly, IP_{av} for phenethylamine and its methoxylated derivatives correlates more closely with association constants for complexes of the corresponding amphetamines and 1,4-dinitrobenzene than IP_1 alone.[39] Here, the α-methyl group of the amphetamines is assumed to have little or no effect on the aromatic ionization potentials.

The activities of tryptamines are less well correlated by IP_{av} than are the activities of phenethylamines, but not many points are available at this time. The point due to 5-methoxy-*N*,*N*-dimethyltryptamine (**18**) seems particularly out of line, both on account of the low IP's of this molecule and because of the chemical similarities (and expected activity similarities, except

for side-chain oxidation by MAO[6]) to 5-methoxytryptamine.

All of the tryptamines have a number of low-energy IP's, so that an average encompassing more IP's might seem more appropriate. However, the third and fourth IP's are relatively constant for these compounds, other than LSD, so that their exclusion from the average is not a serious deficiency.

Despite the complexity of drug interactions and the elusive concept of drug activity, Figure 13 shows that there is probably a significant relationship between behavioral activity (at least in rats) and the electron-donating ability of the phenethylamines and tryptamines. The fact that both classes of compounds seem to fall on the same line may be coincidence, however, since these two classes may bind to different receptors.[40] On the other hand, the receptors might well be similar except for the shape of the molecule permitted to occupy the receptor. If such were the case, then a single correlation of the type found here would be observed. Smythies and co-workers have proposed a single receptor model for activities of all hallucinogens.[41]

Although there are insufficient data at this time to establish a quantitative relationship between hallucinogenic activity and ionization potential, from Figure 13 we note that the drugs with low IP_{av}'s are recognized hallucinogens. For example, in terms of human dosage data, the relative hallucinogenic activity (and IP_{av}'s) of amphetamine, 4-methoxyphenethylamine, 3,4-dimethoxyphenethylamine, mescaline, 5-methoxydimethyltryptamine, and LSD are 0 (9.09 eV), <1 (8.68), <0.2 (8.44), 1 (8.18), >31 (7.70), and 3700 mu (7.64), respectively.[46] A quantitative relationship between dosage measurements of hallucinogenic activity and a parameter which reflects electronic interactions at the active site, in this case IP_{av}, must involve, at the very minimum, a parameter, such as a partition coefficient, which reflects differences in transport of the agents to the active site. Such an analysis awaits the investigation of the photoelectron spectra of an extensive series of psychoactive drugs.

Similarly, for several different types of psychoactive agents, there is an emerging correlation between increasing ability to displace specifically bound [^{3}H]-d-LSD in rat brain homogenates ($-\log ED_{50}$) and decreasing IP_{av}.[47] The $-\log ED_{50}$ activities (and IP_{av}'s) are 4.40 (8.18 eV) for mescaline, 6.52 (7.90 eV) for *N,N*-dimethyltryptamine, 7.00 (7.73 eV, IP_{av} approximated from that of promazine) for promethazine, 7.00 (7.71 eV) for chlorpromazine, and 8.22 (7.65 eV) for d-LSD.[44] Presumably, the ability of a molecule to displace LSD from its binding site stems from its ability to mimic the electronic interactions of LSD with the site.

Although a correlation between the average IP's and activities (MEBL's) of these drugs is consistent with a charge-transfer mechanism where the electron-donor aromatic ring complexes with an electron acceptor at the receptor site, this does not rule out other modes of drug action such as electrophilic aromatic substitution at the aromatic ring (e.g. hydroxylation) or hydrogen bonding to the aromatic ring. However, the better correlation of average IP's than first IP's is consistent with the idea that the aromatic ring serves as a donor in some type of donor–acceptor complex, with stronger donor ability leading to greater activity. As shown earlier, a correlation with IP would also be consistent with stabilization of a donor–receptor complex by dispersion interactions (expected curvature in the plot could be undetectable over the range of IP's investigated). A correlation between reactivities or activities and the aromatic IP's of the series of molecules discussed here does seem to indicate that the frontier molecular orbitals of these molecules are important in determining the reactivity or activity of the molecule. Whether or not charge transfer is the mechanism of complex stabilization is not proven by these correlations, but the importance of frontier orbitals seems assured. Weinstein and co-workers have shown that the electrostatic potentials about the aromatic portion of indolealkylamines are influenced more by the HOMO of the molecule than by other orbitals.[42]

In our discussion, we have neglected the n_N IP. Although this will have some influence on amine basicity, at the physiological pH (7.4) the amino group is protonated, rendering the lone pair unavailable for further interaction. Little is known about the mechanism of action of these drugs; however, hydrogen bonding between the protonated amino group of the drug and a phosphate group of an ATP molecule is believed to be involved.[7,8] In the active site, an additional binding interaction between the aromatic group of the drug and an electrophilic center can then take place, enhancing the activity of the drug in proportion to the electron donor ability of the aromatic ring. The effect of protonation of the amino group on the IP's of the aromatic moiety may be quite large, but calculations by Martín and co-workers indicate that the charge distribution and HOMO energy of a model protonated drug-receptor associate (phenethylamine H^+-H^-) are similar to those of the free base (phenethylamine), but differ considerably from those of the protonated drug itself (phenethylamine H^+).[8] Weinstein and co-workers have similarly shown that the electrostatic potentials of tryptamines and of protonated tryptamines with a hydroxide ion hydrogen bonded to the ammonium group, are essentially identical.[42]

The role of side-chain conformation in determining drug activity is the subject of many current investigations.[7,8,43] While our data indicate no specific interactions of the side chain with the aromatic ring in phenethylamines and tryptamines, the broadness of the bands in the ethylamine-substituted compounds, as compared to unsubstituted or methyl-substituted analogues, is indicative of the presence of many energetically accessible side-chain conformations in the gas phase.

Studies on a greater variety of phenethylamines and tryptamines are in progress to establish whether IP's are statistically valid indicators of drug activity.

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A Photoelectron Spectroscopic Study of Some Pentacarbonylchromium Carbene Complexes

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Abstract: Nine pentacarbonylchromium carbene complexes have been studied via photoelectron spectroscopy and molecular orbital calculations. These studies indicate that amino carbenes are poorer π acceptors than methoxy- or thiomethylcarbenes and that all of the carbene ligands studied are poorer π acceptors than the carbonyl ligand. These results are in accord with predictions of relative π acceptor strength based on structural studies of transition metal carbene complexes. In contrast, our results disagree with the generally accepted view of the carbene carbon as an electron deficient center. In every case, the charge on the carbene carbon was found to be less positively charged than the carbonyl carbons. The stability of the chromium–carbene carbon bond was found to depend upon the charge of the carbene carbon and upon the amount of carbon lone pair character in the bond.

In recent years, there has been considerable interest in carbene species, $\ddot{C}(X)Y$, as ligands in transition metal complexes.[1,2] A good deal of attention has been focussed upon the relative ability of the carbene ligand to act as a π acceptor.[3,4] However, no systematic study of the effects of varying X and Y upon the electronic structure of a series of organometallic carbene complexes has been reported. In order to assess these effects, we have obtained the photoelectron spectra of several pentacarbonylchromium carbene complexes, $(CO)_5CrC(X)Y$ ($X = OCH_3, SCH_3, N(CH_3)_2, NH_2$, $Y = CH_3$; $X = OCH_3, NH_2$, $Y = C_4H_3O$; $X = OCH_3, N(CH_3)_2, NH_2$, $Y = C_6H_5$). In addition we have performed molecular orbital (MO) calculations on these molecules. Those aspects of the MO results which are relevant in the interpretation of the photoelectron spectra will be reported here. A fuller discussion of the MO results will be presented in a separate paper.[5]

Photoelectron spectroscopy (PES) has been shown to be a powerful tool for probing the electronic structure of transition metal complexes, especially when combined with molecular orbital calculations[6] and curve-fitting techniques.[7] Interpretation of the photoelectron spectra of large molecules is often difficult. In species with many valence electrons and complex electronic structures, the peaks that appear in the spectrum tend to be broad, with vibrational structure poorly resolved at best. In addition, peaks corresponding to nearly degenerate MO's may merge into one band. As a result, special techniques are needed for the determination of the maxima of all the peaks which contribute to a band. These maxima are the ionization potentials (IP's) of the orbitals to which the peaks correspond.

A single peak in a photoelectron spectrum should have the shape of a Gaussian distribution. Overlapping peaks may give