Photoelectron Spectra of Psychotropic Drugs. 6. Relationships between Physical Properties and Pharmacological Actions of Amphetamine Analogues

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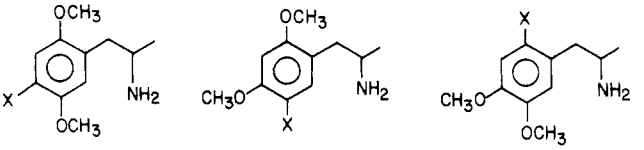
The valence ionization potentials of seven additional members of a series of 2,4,5-trisubstituted amphetamines (1-phenyl-2-aminopropanes) were measured by UV photoelectron spectroscopy. These and previously published data provide experimental measures of the gross electron-donor ability of the aromatic rings of 23 amphetamines. Analogues bearing the 2,5-dimethoxy orientation were found to possess the lowest ionization potentials (IPs); for the analogously X-substituted compounds, the IPs increased in the order 2,5-$(OMe)_2$-4-X < 2,4-$(OMe)_2$-5-X < 4,5-$(OMe)_2$-2-X. Relationships between human psychotomimetic activity (MU), rabbit hyperthermia (SRU), serotonergic receptor affinity (pA_2), and charge-transfer complex stabilities (K_{DNB}) were evalulated statistically. A good correlation ($r^2 = 0.92$) was established between the human and rabbit potencies, but poorer correlations were obtained between animal potencies and pA_2's ($r^2 = 0.68$–0.69) or K_{DNB}'s ($r^2 = 0.03$!). Analyses of the regression relationships between these pharmacological measures and two physical properties, IP and lipid solubility (as modeled by log P), were explored. In general, greater potency is associated with decreasing IP and increasing log P. However, numerous exceptions to single parameter regressions are found. The unusually great potency of the 2,5-$(OMe)_2$-4-X analogues, while qualitatively related to the physical properties, is quantitatively underestimated by these predictors. However, inclusion of a parameter (π_4) which explicitly acknowledges the type of the 4-substituent leads to much improved correlations. These results support previous suggestions that 4-substituents interact directly with the receptor.

Substitution of the phenyl group of amphetamine with one or more electron donors results in derivatives which are, in many instances, potent psychotomimetic agents.[2a] Extensive exploration of these analogues has shown that amphetamines bearing methoxy substituents in the 2 and 5 positions and either alkyl, halo, alkoxy, or thioalkoxy groups in the 4 position are particularly active in man and in a variety of animal assays.[2b-f] Previous studies of physical parameters, such as charge-transfer complex stability,[3a] UV absorption,[3b] and UV fluorescence,[3c] have suggested that electronic factors are relevant to the mechanism of pharmacological actions of these compounds. Molecular orbital indexes, such as the highest occupied molecular orbital (HOMO) energy, are sometimes successful in correlating activities of amphetamines and other psychoactive arylalkylamines,[4] but these computed quantities are dependent upon the method of calculation and upon the choice of geometries chosen for methoxy substituents.[5,6] Unambiguous determination of the ionization potential (IP), which is related to the HOMO energy, is obtained from photoelectron spectra;[6] additionally, important information concerning the conformation of the aromatic substituents in these molecules can be obtained.[5a,6e] Using this technique, we previously established correlations between the IPs of a limited series of methoxy-substituted amphetamines and the psychotomimetic potency of these molecules in man.[6d,e]

In this investigation, we have examined the photoelectron spectra of an expanded series of amphetamine derivatives. We report experimentally measured IPs and analyses of the effects of substituents upon the electronic characteristics of the aromatic nucleus. Two classes of analogues have been considered: (1) a series of methoxy-substituted compounds[6] and (2) three sets of congeners bearing the substituent patterns 4-X-2,5-dimethoxy, 5-X-2,4-dimethoxy, and 2-X-4,5-dimethoxy (where X = OCH_3, SCH_3, CH_3, and Br).



We have also carried out linear regression analyses in order to determine whether the ionization potentials

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Figure 1. Shapes of two highest occupied atomatic π orbitals of benzene. Nodal properties (dashed lines) are preserved in amphetamines, although rigorous symmetries are destroyed.

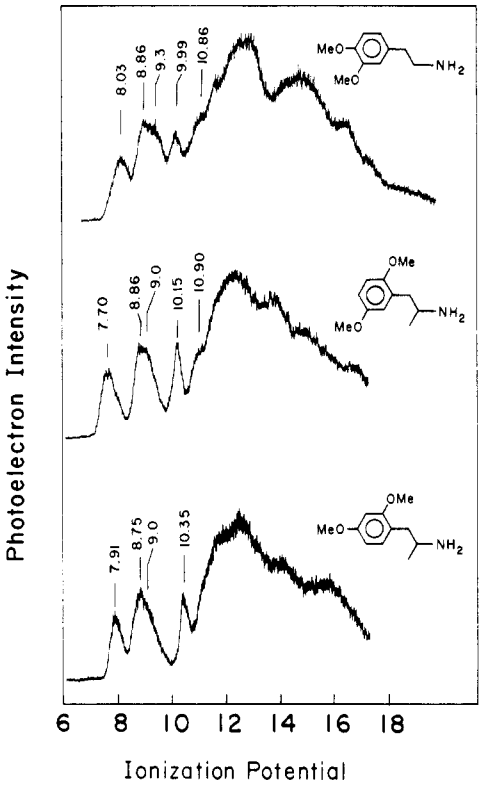

Figure 2. Photoelectron spectra of 3,4-, 2,5-, and 2,4-dimethoxyamphetamine.

and/or octanol–water partition coefficients (log P)[7] are related in any significant way to various types of pharmacological actions of these compounds, namely, the psychotomimetic activities in man (MU), hyperthermic potencies in rabbits (SRU), and serotonin receptor affinities in the isolated rat stomach fundus assay (pA_2). In response to the suggestion of a referee of the original manuscript, we have also carried out linear-regression analyses using a variable (the π value), which reflects the lipophilicity of the X substituent.

Results and Discussion

Photoelectron Spectra.[8] Amphetamine, whose photoelectron spectrum we have reported earlier,[6a] has two high-lying molecular orbitals which give rise to two low-lying ionization potentials. These are both localized on the aromatic moiety. Figure 1 shows the symmetry and localization property of these aromatic orbitals. The filled and open circles represent plus and minus coefficients in the LCAO–MO wave functions, and the radius of each circle is proportional to the coefficient at that site in the MO. In amphetamine, the difference between the energies of these two orbitals is small, but substitution of more powerful donors, such as methoxy groups, has a more profound influence on these orbitals, splitting the degeneracy and orienting these orbitals so that the HOMO has the largest coefficient at the site of methoxy substitution.

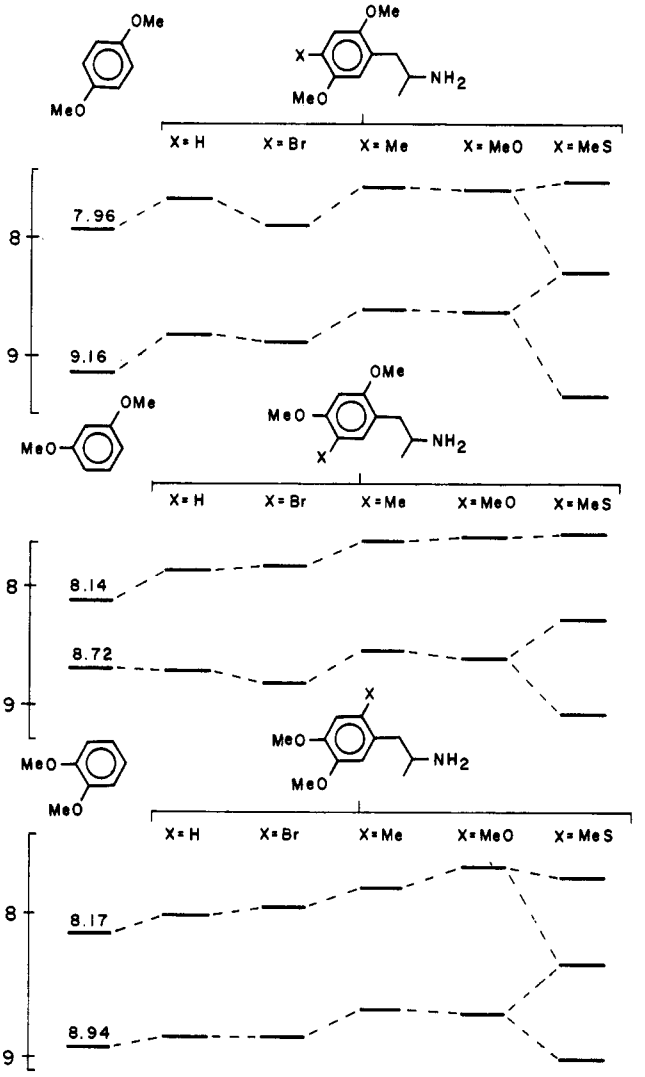

Figure 3. Correlations between π IPs of dimethoxybenzenes and corresponding dimethoxy-X-amphetamines, where X = H, Me, MeO, MeS, and Br.

The bands associated with ionization of the amine lone pair occur in the 8.9–9.2 eV region and are frequently obscured by overlapping ionization bands from the aromatic π orbitals and the oxygen lone-pair combination orbitals.[6] These assignments are based upon comparisons with phenethylamine lone-pair ionizations (9.2–9.5 eV)[6a] and are consistent with the observed 0.2-eV shift to lower ionization energies observed for α-methyl substitution of primary amines (cf. ethylamine IP_n = 9.50 eV; isopropylamine IP_n = 9.31 eV).[9]

The spectra of three isomeric dimethoxyamphetamines (DMAs) are shown in Figure 2, and the low-energy ionization potentials and assignments are tabulated in Table I. The aromatic regions of the spectra resemble very

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(8) Photoelectron spectra were determined at LSU by L.N.D. with a Perkin-Elmer PS-18 photoelectron spectrometer using xenon and argon as internal calibrants. Peak positions are taken as the maximum of each band and are accurate to ±0.05 eV. Calculations summarized in Figure 8 were carried out using the STO-3G basis set and were described in more detail earlier.[6e] Samples were, for the most part, made available from the UCSF laboratories.

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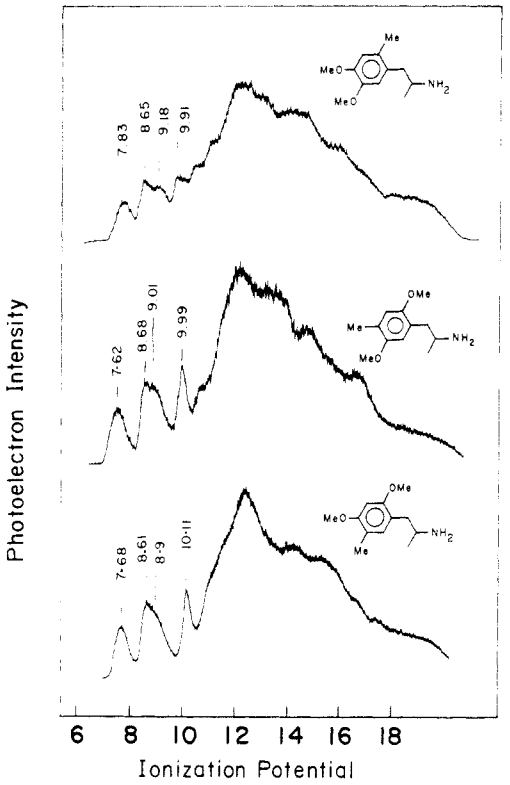

Figure 4. Photoelectron spectra of dimethoxymethylamphetamine.

closely those of the corresponding dimethoxybenzenes, which we have analyzed in detail elsewhere.[5a,6e] Figure 3 shows the correlation between the first two π IPs of each isomeric dimethoxybenzene and the corresponding amphetamines studied here for each series. The IP changes caused by attachment of the side chain to form the amphetamine have been analyzed earlier[6e] and are a function of the magnitude of the orbital coefficient at the site of attachment.

In the DMAs, the amine lone-pair ionizations appear as broad bands at 9.3, 9.0 and 9.0 eV in the three compounds in Figure 2. In addition, one or two relatively sharp oxygen lone-pair ionizations can be observed in the 9.9–10 eV region of the spectra. The broadness of the bands in the 3,4-DMA spectrum and the relatively low IP of one oxygen lone pair indicate that this molecule, like *o*-dimethoxybenzene,[5a] has at least one nonplanar methoxy group. Similar suggestions of nonplanar methoxy have been made on the basis of serotonin receptor affinities.[10c]

The effects of substitution of a methyl, methoxy, methylthio, or bromo substituent upon each of the dimethoxyamphetamines can be discerned from the photoelectron spectra shown in Figures 4–7 and from the correlation diagrams given in Figure 3.

The dimethoxymethylamphetamines (Figure 4) have π IPs which are 0–0.2 eV lower than those of the dimethoxy compounds. Otherwise, the spectra of the dimethoxy and dimethoxymethyl series are extremely similar, even in the σ ionization region (11–18 eV) of the spectra. Like 3,4-dimethoxyamphetamine and *o*-dimethoxybenzene, 4,5-dimethoxy-2-methylamphetamine has broad bands due to nonplanarity induced by *o*-methoxy groups. The low IP of the oxygen lone pair in DOM (2,5-dimethoxy-4-methylamphetamine) and the broadness of the first band may indicate that some of the nonplanar methoxy conformers are present in this compound as well. Based on our previous arguments,[5a] the 5-methoxy group is more likely to be nonplanar than the 2-methoxy group in DOM.

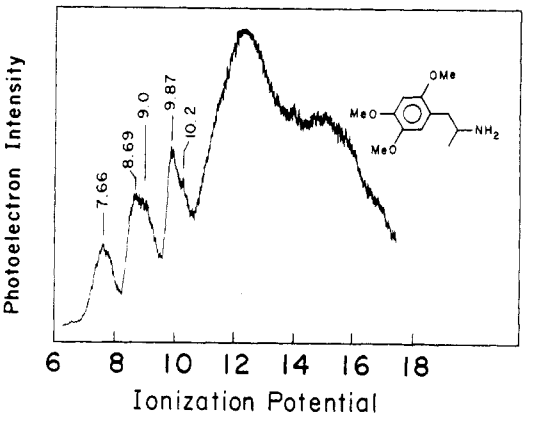

Figure 5. Photoelectron spectrum of 2,4,5-trimethoxyamphetamine.

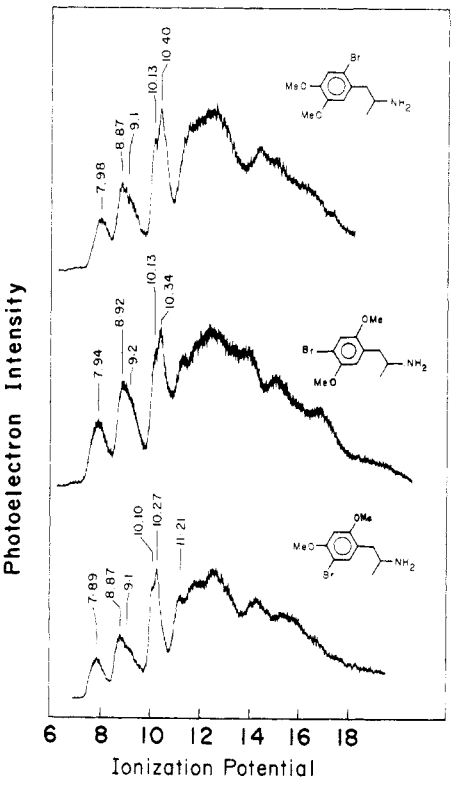

Figure 6. Photoelectron spectra of bromodimethoxyamphetamines.

The spectrum of 2,4,5-trimethoxyamphetamine, shown in Figure 5, closely resembles that of 2,5-dimethoxy-4-methylamphetamine. We have argued previously that the 5-methoxy group is preferentially nonplanar in this molecule,[5a] and the broadness of the first band and low energy of the n_O IP at 9.9 eV also provide support for this conclusion.

The bromodimethoxyamphetamine spectra, shown in Figure 6, are again quite similar to those of the dimethoxy compounds, except for additional strong bands in the 10.2–10.4 eV region of the spectrum. These strong bands are attributed to bromine lone-pair ionizations which occur

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Table I. Ionization Potentials and Assignments, Partition Coefficients, Hallucinogenic Activities, and Binding Affinities of Amphetamine Derivatives

substitution pattern	IP_1 [a]	IP_2 [a]	other resolved IPs [a]	log P [b]	human hallucinogenic act., [c] MU	rabbit hyperthermic potency, [d] SRU	serotonergic receptor affinity, [e] pA_2	DNB complexation, [f] K_{DNB}
amphetamine	8.99	9.35	9.0 (n_N)	1.63		1.3, ~1 [k]	5.27	0.55
2-OMe	8.24 [g]	8.93					5.54	0.83
3-OMe	8.28 [g]	8.93					5.92	0.96
4-OMe	8.16	9.19		1.77	4		5.16	1.02
2,3-$(OMe)_2$	8.30* [g]	8.72					5.54	
2,4-$(OMe)_2$	7.91	8.75	9.0 (n_N), 10.35 (n_O)	1.75	5	2.5	5.60	1.32
2,5-$(OMe)_2$	7.70	8.86	9.0 (n_N), 10.15 (n_O)	1.88, 1.72	8	2.7	6.83	1.39
2,6-$(OMe)_2$	8.18	8.18	8.93 (n_N), 10.6 (n_O), 10.84 (n_O)				5.09	1.49
3,4-$(OMe)_2$	8.03	8.86	9.3 (n_N), 9.99 (n_O)	1.00, 1.20	<1	<<0.3	5.45	1.95
3,4-methylenedioxy	8.01	8.97	9.1 (n_N), 10.69 (n_O)	1.63	3	2.5 [l]	6.45	0.68
2,3,4-$(OMe)_3$	8.09	8.36	8.9 (n_N), 9.77 (n_O), 10.23 (n_O)	1.36	<2	<<0.3 [l]	5.07	1.7
2,4,5-$(OMe)_3$	7.66	8.69	9.0 (n_N), 9.87 (n_O), 10.2 (n_O)	1.74, 1.10	17	11.8	6.81	2.43
2,4,6-$(OMe)_3$	7.76	8.19	8.8 (n_N), 9.79 (n_O)	1.57	10	3.1 [l]	6.28	2.09
3,4,5-$(OMe)_3$	8.16	8.16	9.2 (n_N), 9.77 (n_O), 10.19 (n_O)	1.48	2.2	3.6 [k]	5.60	3.14
4,5-$(OMe)_2$-2-Me	7.83*	8.65	9.2 (n_N), 9.91 (n_O)	1.66 [i]		0.5	5.86 (±0.18)-3 [m]	
2,5-$(OMe)_2$-4-Me	7.62	8.68	9.0 (n_N), 9.99 (n_O)	2.08, 2.24	80	100	7.12	
2,4-$(OMe)_2$-5-Me	7.68*	8.61	8.9 (n_N), 10.11 (n_O)	2.31 [i]		0.9	5.61 (±0.04)-2 [m]	
4,5-$(OMe)_2$-2-SMe	7.75, 8.49*	9.1	9 (n_N), 10.1 (n_O)	1.71 [i]		1.7	n	
2,5-$(OMe)_2$-4-SMe	7.64, 8.37	9.42	9.1 (n_N), 10.11 (n_O), 10.68 (n_O)	2.17 [i]	50	53.9		
2,4-$(OMe)_2$-5-SMe	7.64, 8.40*	9.2	9.09 (n_N), 10.22 (n_O)	2.22 [i]		2.8	5.77 (±0.09)-2 [m]	
4,5-$(OMe)_2$-2-Br	7.98*	8.87	9.1 (n_N), 10.13 (n_O), 10.40 (n_{Br})	1.96 [i]		3.4	5.75 (±0.05)-2 [m]	
2,5-$(OMe)_2$-4-Br	7.94	8.92	9.2 (n_N), 10.13 (n_O), 10.34 (n_{Br})	2.58, 2.54 [h]	400	405 [k]	7.35	
2,4-$(OMe)_2$-5-Br	7.89*	8.87	9.1 (n_N), 10.10 (n_O), 10.27 (n_{Br})	2.61 [i]	4 [j]	2.3	n	

[a] Vertical IPs (±0.06 eV); those marked with an asterisk are reported here for the first time. Others were reported in ref 6d. [b] P = experimentally determined octanol/water partition coefficient reported in ref 7b, unless otherwise noted. When two values are given, the first was used in the correlations reported in Tables IV–VIII. [c] Human data relative to mescaline ≡1 MU.[2a] [d] Determined in the rabbit according to method A relative to DOM = 100 SRU.[5b] [e] Determined in the isolated rat stomach fundus assay; unless otherwise noted, all values are taken from ref 10c. New values are reported, followed by standard deviations in parentheses and the number of determinations. [f] Equilibrium constant for DNB complex formation.[3a] [g] Ionization potentials estimated from those of the correspondingly substituted toluenes. Values for 2-methoxytoluene were taken from ref 6a, and those for 3-methoxytoluene were from Kobayashi, T.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2563; the values for 2,3-dimethoxytoluene are reported here for the first time. [h] Experimentally determined values reported by Nichols et al.[7b] [i] Calculated values reported in Anderson et al.[5b] [j] Sepulvada, S.; Valenzuela, R.; Cassels, B. K. *J. Med. Chem.* **1972**, *15*, 413. [k] Aldous et al.[2e] [l] Reported by Anderson et al.[5a] [m] New values. [n] pA_2 cannot be accurately determined due to high degree of agonism elicited by these compounds on the rat fundus preparation.

Table II. Regression Analyses of Charge-Transfer Complexation (K_{DNB}), Serotonin Receptor Affinities (pA_2), Rabbit Hyperthermia (SRU), and Hallucinogenic Activity (MU)

correlation equation [a]	n	r^2	sig	F	SD
(1) log MU = 0.13 (±0.71) log K_{DNB} + 0.59 (±0.20)	9	0.01	0.97	0.04	0.41
(2) log MU = 0.77 (±0.18) pA_2 − 3.83 (±1.10)	11	0.68	0.001	19.0	0.45
(3) log MU = 0.77 (±0.11) log SRU + 0.40 (±0.11)	12	0.92	0.0001	115.6	0.23
(4) log SRU = 0.35 (±0.76) log K_{DNB} + 0.21 (±0.22)	9	0.03	0.82	0.2	0.54
(5) log SRU = 1.01 (±0.19) pA_2 − 5.59 (±1.14)	15	0.69	0.001	29.0	0.49
(6) pA_2 = 0.43 (±0.84) log K_{DNB} + 5.17 (±0.21)	13	0.02	0.77	0.3	0.65

[a] n = number of compounds in correlation; r^2 = variance; sig = significance level; F = F test; SD = standard deviation of regression; numbers in parentheses are standard deviations.

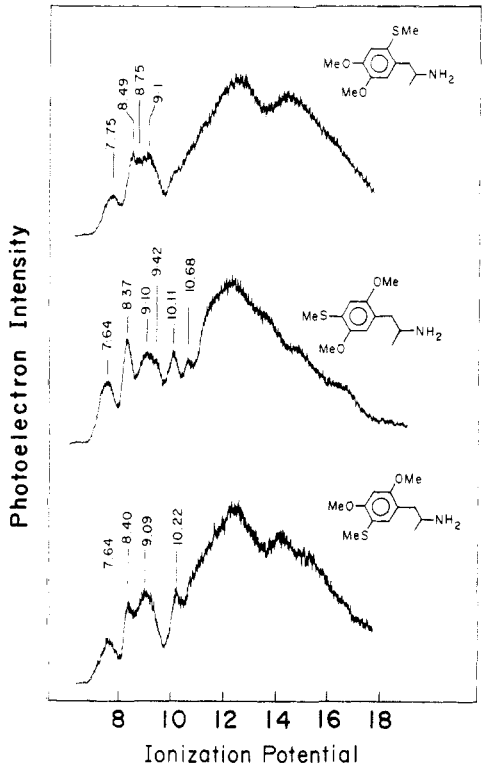

Figure 7. Photoelectron spectra of dimethoxymethylthioamphetamines.

at 10.2–10.7 eV in alkyl bromides[11a] and at 10.16 eV in bromobenzene.[11b] A bromo substituent can either raise or lower ionization potentials of π systems. For example, the first IP of benzene is lowered by 0.2 eV by a bromine substituent, while the second is raised by 0.4 eV.[11b] This is a consequence of the well-known dichotomy between inductive electron withdrawal and resonance electron donation by bromine (and other halogens). When attached at a site with a large MO coefficient, bromine raises the MO energy (lowers the IP), since resonance electron donation is the dominant effect. If attached at a node or site of small orbital coefficient, bromine lowers the orbital energy (raises the IP), since inductive electron withdrawal dominates. The attachment of bromine to 2,5-DMA causes a large increase in the first IP, since Br is attached at a site of small coefficient. The 2,5-DMA highest occupied molecular orbital resembles the first orbital in Figure 1, with large coefficients at the sites of methoxy substitution. The second IP of 2,5-DMA, the first IP of 2,4-DMA, and both IPs of 3,4-DMA are unaffected by bromine substitution within experimental error. The second IP of 2,4-DMA is increased. These changes are all compatible with previously calculated coefficients for these orbitals (see Figure 8).[6e]

Finally, the spectra of the methylthiodimethoxyamphetamines (Figure 7) are quite different from those of the other compounds discussed here, since the methylthio group itself has high-lying lone-pair orbitals which give rise to ionization potentials in the same region as the aromatic IPs. For example, dimethyl sulfide has a sulfur lone-pair IP of 8.67 eV.[12] In thioanisole, this lone-pair orbital mixes strongly with one of the benzene highest

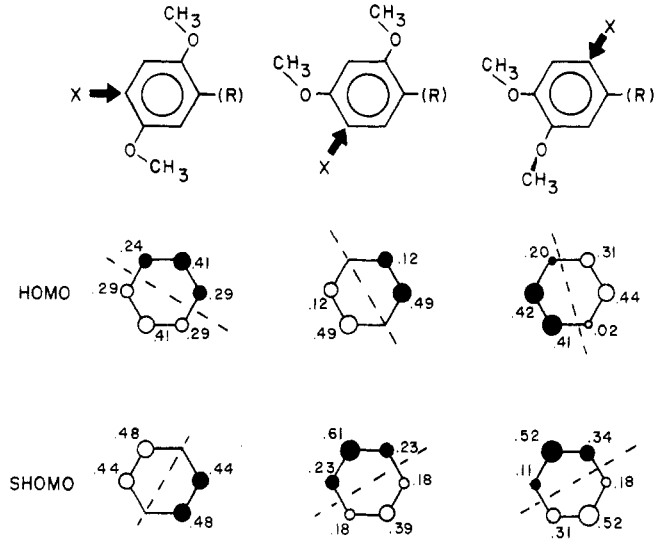

Figure 8. STO-3G orbital shapes for *o*-, *m*-, and *p*-dimethoxybenzene.[6e]

occupied orbitals to produce two orbitals having IPs of 8.02 and 10.20 eV[13] (or 8.07 and 10.14),[14] while the other HOMO of benzene remains unchanged in energy. Whereas the compounds described previously have only two aromatic IPs below 9.5 eV, the methylthio compounds have three, and all should have significant density on the sulfur lone-pair orbital. Thus, the correlations shown in Figure 3 suggest that the three IPs in the thio analogue correlate with two in the other dimethoxy compounds.

The rotational barriers of methylthio groups attached to aromatic rings are quite small (~1 kcal/mol),[13] so that thioanisole consists of both planar and nonplanar conformers in the gas phase. Based on our previous arguments, a methoxy group should tend to make a methylthio (like a methoxy) group nonplanar in the order ortho > para > meta. The 5-thiomethoxy compound has methoxy groups both ortho and para to the methylthio substituent, and there should be a strong tendency for nonplanarity of the methylthio moiety in this compound. In fact, the spectrum of this molecule shows broad bands characteristic of the presence of several conformers, and the IP of this molecule is only 0.3 eV lower than that of 2,4-dimethoxyamphetamine itself. This seems at first glance quite unusual, since the IP of benzene is lowered by 1.2 eV by the methylthio group.[13,14] However, a *p*-thiomethyl group lowers the IP of thioanisole by only 0.14 eV; that is, thiomethyl only weakly donates electron density to an already electron-rich system.

The 2,5-dimethoxy-4-(methylthio)amphetamine has essentially the same first IP as the 2,5-dimethoxy compound, which is consistent with a small coefficient in the HOMO at the site of methylthio substitution, a fact borne out by ESR spectra of the corresponding radical cation of 1,4-dimethoxybenzene.[14] The 2-methylthio group lowers the first IP of 3,4-dimethoxyamphetamine by 0.28 eV. In the last compound, the anomalous oxygen lone-pair IP of 9.9 eV is still present, suggesting that one of the methoxy groups remains nonplanar.

In all the series described here, the *p*-dimethoxy substituent pattern clearly causes the benzene ring to have lower ionization potentials than either the ortho or meta, and the orbital localization caused by the *p*-dimethoxy

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groups causes substituents at the 4 position of 2,5-dimethoxyamphetamines to have a much smaller influence on orbital energies than does substitution of the same functionalities at the 2 position of 4,5-dimethoxyamphetamine. We have discussed the MO's of dimethoxybenzenes in some detail elsewhere.[5a,6e] For the purpose of this report, these are reproduced in Figure 8. These numbers are orbital coefficients in the highest occupied and second highest occupied molecular orbitals (HOMO and SHOMO).[6e] The species are drawn in such a way as to emphasize the similarities of nodal properties of HOMO and SHOMO of the DMAs when the side chain is attached to the right-most carbon. The arrow shows the site of substitution to form the 2,4,5-trisubstituted amphetamines. The first IP of *p*-dimethoxybenzene is the lowest of the three compounds because both methoxys are located at sites of maximum HOMO coefficients in benzene. Similarly, the second IP of the ortho compound is the highest of the three because of reltively small coefficients at the sites of substitution.

These orbital localizations are also useful in rationalizing the trends shown in Figure 3. Substituents in the 4 position of 2,5-dimethoxyamphetamine cause the least change in the first IP because of the small coefficient at this site. Only bromine significantly increases the IP, for the same reason. The second IP of 2,5-DMA is influenced greatly by substitution at carbon-4 because of the relatively large coefficient in the SHOMO. In the other two amphetamines, substituents have a relatively large effect on the first IP and small effect on the second IP. Once again, coefficient magnitudes (Figure 8) show why this is so.

Pharmacological Evaluation and Correlations between Various Pharmacological Activities. The pharmacological potencies (MU[15a] and SRU[15b]) measured in whole animal assays are given in columns 6 and 7 of Table I, the serotonin receptor affinities (pA_2[15c]) are given in column 8, and data on the equilibrium constant for complexation with *p*-dinitrobenzene (K_{DNB})[3a] are given in the last column. The most potent analogues in human, rabbit, or binding studies are the 2,5-dimethoxy-4-X-substituted compounds. Whereas addition of a methyl, thiomethyl, or bromo group into the 4 position of 2,5-dimethoxyamphetamine results in dramatic increases in potency, introduction of these substituents into either 2,4- or 4,5-DMA produces only minor alterations in activity.

Table II presents linear regressions between various pharmacological measures of activity and between these and the DNB complexes. The human psychotomimetic and rabbit hyperthermic potencies are highly correlated with each other, and both are less well correlated with pA_2 values. However, a strict correlation between these data cannot be expected since, in contrast to the whole animal assays, the isolated rat fundus preparation possesses different metabolic and distributional characteristics.[16] DNB complex stabilities correlate with none of the pharmacological measures. Sung and Parker reported a good correlation between human activities and K_{DNB}, but only by deleting three of the nine compounds from the correlation.[3a] Even if some type of molecular complexation occurs between the aromatic rings of amphetamines and the receptor site, the stabilities of DNB complexes do not parallel receptor affinities. On the other hand, the correlations between MU and SRU, and to a lesser extent between MU and SRU and pA_2, implies that the various responses measured are related to at least the same gross structural features of the amphetamines. This result is not unexpected, since numerous pharmacological studies have implicated the involvement of serotoninergic mechanisms in both behaviorial[17,18] and thermoregulatory[19] disruptions. Thus, all of these pharmacological measures are at least loosely related, and the similar rankings of potency of compounds toward these various tests are expected.

There is an additional fundamental reason why whole animal or human activities are not expected to correlate with receptor binding assays: not all substituted amphetamines produce the same type of psychotomimetic effect, indicating that more than one mechanism of action is exhibited by these compounds.[10f] Thus, amphetamines may range in activity from stimulant to truly hallucinogenic, and studies in serotonin-trained rats indicate that generalization occurs only with the highly substituted (e.g., DOM) amphetamines.[10e]

Investigations of Quantitative Structure–Activity Relationships (QSAR) for Amphetamines. Shulgin has observed that 2,5-dimethoxyamphetamines exhibit anomalously high potencies in humans as compared to isomeric derivatives.[2b] The number of methoxy groups seems also to influence activity, since the order of hallucinogenic potencies is more or less trimethoxy > dimethoxy > methoxy > unsubstituted, regardless of the position of the substituent. These rough, but simple, structure–activity relationships have encouraged QSAR studies which have met with considerable success. However, since both the number and positions of substituents influence all structural and physical parameters to some extent, it is possible not only to discover meaningful QSARs but to find meaningless ones as well. We have, nevertheless, carried out linear regression analyses to determine whether ionization potentials, octanol–water partition coefficients,[20,21]

(15) (a) In humans, psychotomimetic potency (mescaline units) is defined with reference to the psychological state induced by mescaline.[2a,b] Titration of the potency of an unknown compound involves assay of a series of graded doses and, subsequently, determination of the doses required to produce "just noticable" and "maximally effective" effects. The average of these doses for mescaline (3.75 mg/kg) divided by this average for the compound in question is the activity measure in mescaline units (MU). Accuracies of the values have been estimated at about 25%.[7a] (b) In the rabbit hyperthermia assay, activity (standard rabbit units) is defined in terms of the dose necessary to product a 1 °C temperature rise.[2e,8] Determination of this dose is from log dose–Δ temperature plots. Division of this dose by the DOM dose (0.27 μmol/kg) gives the hyperthermic potency relative to DOM = 100 SRU. Values reported here are generally accurate to about 5–10% as ascertained from the dose–response plots.[2d,e] (c) Serotonin receptor affinities (pA_2's) are determined by competition experiments in which drug competes with serotonin for occupation of the serotonergic receptor sites in the rat stomach fundus.[10a–c] Uncertainties of the measurements are <5% as ascertained from the log dose–response plots.[10a,16]

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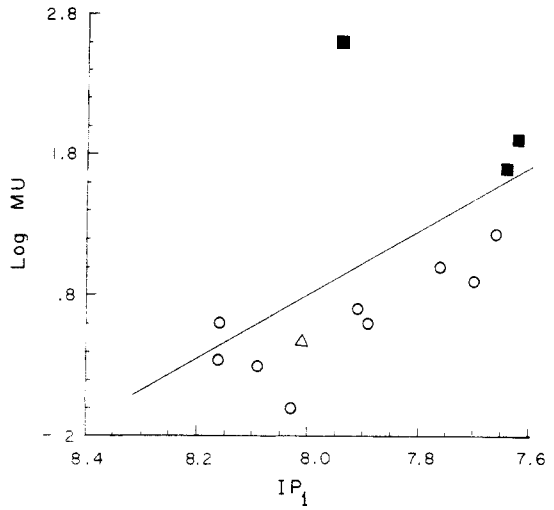

Figure 9. Plot of log MU vs. IP_1. The correlation equation is log MU = −2.14 IP + 17.9. Δ is the point for 3,4-(methylenedioxy)amphetamine and ■ represents points for 4-X-2,5-dimethoxyamphetamines.

and the lipophilicities of the 4-substituents[7b,10b] are related to these pharmacological activities. Most prior regression analyses were developed before the isomeric dimethoxy-X-amphetamines were available. Having accumulated physical and biological data on these compounds, we can now make more demanding tests of relationships between pharmacological potencies and physical properties.

Since we have extensively tested the use of IP and log P parameters separately and together to predict biological activities, it is important to demonstrate that these independent variables are orthogonal. The squared correlation coefficient (r^2) is only 0.12 for these data or 0.18 with amphetamine excluded.

Linear regression analyses for various activities vs. IP_1 and log P yield rather poor results, together (r^2 = 0.34–0.61) or individually (r^2 = 0.08–0.35). We also tested the use of IP_2 and $(\log P)^2$ but found no significant improvements in the correlations. Beginning with the serotonin receptor affinities (pA_2), the log P data are not significantly related to the pA_2 data, and the IP_1 regression with pA_2 is also poor. The best two-parameter equations are no better than the IP equation alone, according to the partial F statistic. There are trends toward increasing affinity with decreasing IP or increasing log P, but even the best equation is a poor predictor of pA_2.

For rabbit hyperthermia, log P is a fair predictor of log SRU for the methoxyamphetamines containing no other substituents, but the significance of this regression degrades considerably upon inclusion of all amphetamines.

For human hallucinogenic activities (log MU), there is a significant bilinear regression with IP and log P if only methoxyamphetamines are included, but using the full data set, much less significance is found. Much of this is due to DOB, which has a high activity but relatively normal IP. Figure 9 is a plot of log MU and IP_1 for the full data set. This regression is remarkably good, except for the point for DOB. However, many of the compounds for which pA_2 and SRU data are available are absent from the set of human activities, so that this "goodness" relative to the fit with pA_2 and SRU is very probably fortuitous. That is, if human data prove to be similar to rabbit hyperthermic potencies for these missing compounds, the significance of the relationship between log MU and IP_1 and log P will break down.

These statistical analyses (and many others tested but not included here) demonstrate the limited nature of the correlations between log P values and IPs and various measures of biological data for substituted amphetamines. The best correlations are found with human data, but the accuracy of these data is believed to be at best ±25%, and the good overall correlation with MU could result from the absence of activity data on several crucial compounds which have relatively low IPs and high log P values. Regressions using either log P or IP, or both, consistently overestimate the potency of the 2,4-$(OMe)_2$-5-X and 4,5-$(OMe)_2$-2-X compounds and underestimate the potencies of the 2,5-$(OMe)_2$-4-X analogues. This trend is seen to a limited extent with the MU and pA_2 data, but is much less pronounced than in the SRU data, most probably due to the small number of 2,4-$(OMe)_2$-5-X and 4,5-$(OMe)_2$-2-X analogues in the full data sets. These results confirm that the 2,5-$(OMe)_2$-4-X compounds possess a potency which is inherently greater than that possessed by other derivatives and which cannot be accounted for in terms of the log P and IP alone.

The insufficiency of IP and log P to describe accurately receptor affinities suggests that the stability of the drug–receptor complex may be governed in part by direct interactions of specific atoms of the aromatic ring with the receptor site[22] or by a direct interaction between substituent and receptor. To test the former hypothesis, we are measuring the ^{13}C chemical shifts of the aromatic carbons of amphetamines to develop parameters for individual ring carbons. The substituent interaction hypothesis has been suggested by both Nichols[7b] and Glennon,[10a] who have postulated that lipophilic substituents located at the 4 position of the amphetamines bind favorably to a lipophilic site in the serotonin receptor.

We have tested this postulate in a manner suggested by a helpful anonymous referee of the 1980 version of this paper. For the lipophilicity of the substituent at the 4 position, the π values (substituent lipophilicities) were used from the Hansch–Leo compilation.[23] A priori, the unusual activities of the 4-X-2,5-DMAs are expected to be accounted for in this way, since the π values of the anomalously active 4-substituents, Me, MeS, and Br, are 0.56, 0.61, and 0.86, respectively, while those of H and MeO are 0.0 (by definition) and −0.02.[21] Table III summarizes the results of these regressions, where π_4 refers to the π values of the substituent at position 4 of the amphetamine. We have tried one, two, and three parameter equations, since log P is related to the efficiency with which the amphetamine reaches the active site, while IP and π_4 are postulated to be related to binding forces at the receptor site.

The parameter π_4 is the best single correlator of any of the three activity measures! However, it is clear that this is due to the fact that there are basically two types of molecules, the relatively inactive compounds, not containing a lipophilic 4-substituent (π_4 = 0.0 to −0.02), and three highly active compounds, having lipophilic 4-substituents (π_4 = 0.56 to 0.86). Inclusion of IP_1 in the cor-

(20) Two forms of log P were tried representing equilibrium state conditions (log P) and non-steady-state conditions $(\log P)^2$; for theoretical derivation of these functional forms, see McFarland, J. W. *J. Med. Chem.* **1970**, *13*, 1192, and Penniston, J. T.; Beckett, L.; Bently, D. L.; Hansch, C. *Mol. Pharmacol.* **1969**, *5*, 333.

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Table III. Regression Analyses of Pharmacological Potencies vs. IP, log P, and π_4

correlation equation	n	r^2	sig	F	SD
pA_2					
(1) $pA_2 = 1.93\ (\pm0.54)\ \pi_4 + 5.81\ (\pm0.13)$	19	0.43	0.002	12.7	0.54
(2) $pA_2 = 1.72\ (\pm0.47)\ \pi_4 - 0.92\ (\pm0.34)\ IP_1 + 13.21\ (\pm2.72)$	19	0.61	0.001	12.5	0.46
(3) $pA_2 = 1.72\ (\pm0.62)\ \pi_4 - 0.92\ (\pm0.41)\ IP_1 - 0.02\ (\pm0.44) \log P + 13.21\ (\pm3.59)$	16	0.62	0.007	6.6	0.49
SRU					
(4) log SRU = $2.67\ (\pm0.37)\ \pi_4 + 0.30\ (\pm0.10)$	18	0.77	0.0001	52.7	0.41
(5) log SRU = $2.60\ (\pm0.38)\ \pi_4 - 0.32\ (\pm0.32)\ IP_1 + 2.80\ (\pm2.54)$	18	0.78	0.001	26.8	0.41
(6) log SRU = $2.36\ (\pm0.42)\ \pi_4 - 0.20\ (\pm0.33)\ IP_1 + 0.35\ (\pm0.29) \log P + 1.25\ (\pm2.81)$	18	0.80	0.001	18.9	0.41
MU					
(7) log MU = $2.11\ (\pm0.31)\ \pi_4 + 0.65\ (\pm0.10)$	13	0.81	0.001	47.0	0.33
(8) log MU = $1.87\ (\pm0.28)\ \pi_4 - 1.04\ (\pm0.45)\ IP_1 + 8.91\ (\pm3.53)$	13	0.88	0.001	36.1	0.28
(9) log MU = $1.63\ (\pm0.32)\ \pi_4 - 0.91\ (\pm0.44)\ IP_1 + 0.31\ (\pm0.22) \log P + 7.37\ (\pm3.56)$	13	0.90	0.001	26.88	0.27

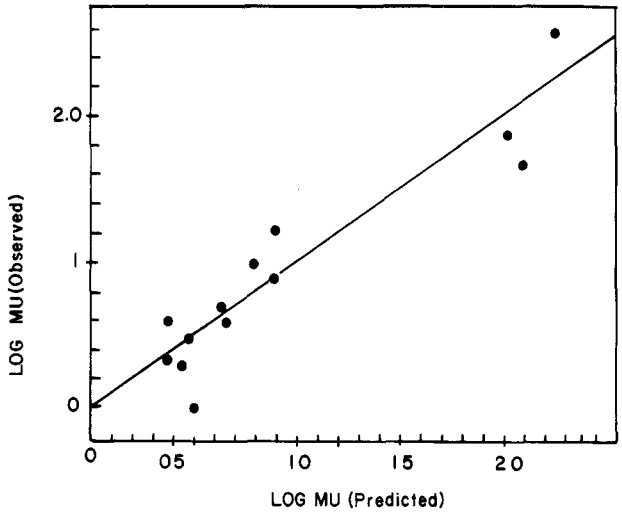

Figure 10. Plot of log MU vs. the values predicted according to eq 8 in Table IV: log MU = $18.7\pi_4 - 1.04IP_1 + 8.91$.

relations does not grossly influence the statistics, but as can be seen from Figure 10, the activity trends for the relatively inactive compounds are now better correlated (log MU = $18.70 - 1.04IP_1 + 8.91$). The inclusion of log P along with π_4 and IP does not improve any of these correlations. It is the lipophilicity of the 4-substituent, not that of the molecule as a whole, which has a significant influence on receptor binding, rabbit hyperthermic effects, and hallucinogenic potency in man. The isomers studied here are especially significant in this regard, since overall lipophilicities are similar, but activities are very different.

Other recent studies have shown that 4-alkyl substituents indeed enhance the serotonin receptor binding affinities of 2,5-dimethoxyamphetamines. The 4-alkyl substituent effect is of the "all or none" variety for alkyl groups from methyl through amyl, with little variation in activity for this whole series.[24]

We conclude that there are two significant indicators of hallucinogenic potency: π_4 of the 4-substituent and, for molecules without a lipophilic 4-substituent, the first ionization potential. Whether or not 4-Me, 4-MeS, or 4-Br substituents fit into lipophilic pockets on the receptor or are simply relatively large and polarizable substituents which weakly attract with a receptor surface site is not known. However, these results imply a "three-site model" for receptor binding involving the (1) ammonium group, (2) electron-rich aromatic ring, and (3) 4-substituent.

Acknowledgment. We are grateful to the National Institute on Drug Abuse for financial support of this work through research Grants DA024221A to K.N.H. and DA-01642 to R.A.G. The statistical analyses were carried out on the PROPHET system, a national resource for the study of chemical–biological interactions sponsored by the National Institutes of Health, Division of Research Resources.

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