actions, an A ring with an *ortho* substituent other than methyl will be constrained to rotation about the SO_2–N bond, whereas an A ring with an *o*-methyl substituent is capable of rotation about the SO_2–N bond as well as the C–N bond of the A ring. This additional degree of rotational freedom is sufficient to change the population distribution of the various rotational isomers and thereby lead to the seemingly "anomalous" S-ring absorption for this compound.[12] Other studies[17] indicate that interaction of the methyl group with the SO_2 group changes the S–O bond character. Thus, both of the latter factors may contribute to the appearance of an "anomalous" pmr S-ring absorbance in the *o*-methyl derivative.

Conclusion.—The persistence of a singlet absorption for the S ring in the N^4-acetylated series (I, II, Y = CH_3CO) and the essentially constant chemical shift for the A-ring protons in the members of the N^4-acetylated and the nonacetylated series strongly suggests that at least for nonacidic or nonionized acidic sulfanilamides, substituted phenyl substituents placed on the sulfonamido nitrogen have extremely little, or none, of their effect transmitted through the SO_2 group. This conclusion is not in agreement with the uv[5] and thermochemical results[6] previously cited.

It appears most likely that the discrepancy between the conclusions of this pmr study and the uv studies has its origin in the changing nature of the photoexcited states of these compounds. In this study only ground-state properties are being measured, while in the latter studies the electronic transition between the ground state and some photoexcited state is being determined. Assuming the electronic ground state to be the same in both instances, the spectral variations observed in the uv studies appear to reflect differences in the excited state properties of the various sulfanilamides. The uv studies could be indicating resonance conjugation in the excited state, the mixing of excited molecular orbitals between the S ring and the A ring when the planes of the latter are situated one above the other, or a combination of these factors. The discrepancy between this study and the thermochemical studies most probably is due to the polymorphic nature of crystalline sulfanilamides. Since the combustion experiments in the latter instance were performed using crystalline sulfanilamides of doubtful crystal structure, it must be inferred that these experiments were reflecting differences in the crystal nature of the compounds rather than fundamental electronic differences.

In conclusion, this study indicates that attempts to correlate the spectral properties of sulfanilamides with their observed bacteriostatic activities will be frustrated by the free rotation allowed about the SO_2–N bond when these compounds are in solution. Quests for such correlations apparently will require that model systems be constructed in which rotation about this bond is prohibited. These compounds, while no doubt biologically inactive or poorly so, should provide a more realistic approximation to the bound form of a sulfanilamide. Comparison of the spectral properties of these model systems with the biological activities of their unrestricted counterparts may thus prove more profitable in seeking correlations and in investigations of the electronic character of bound sulfanilamides.

Acknowledgment.—The authors sincerely thank Dr. William Welstedt, Jr., and Dr. Victor German for their participation in many interesting and illuminating discussions while this work was in progress.

(17) An ir analysis of these compounds has been completed and will be reported in detail at a later date. In solution, the S–O band positions for these N^1-phenylsulfanilamides is a function of their concentration. Extrapolation to zero concentration affords absorption values for the S–O bond which may be considered as independent of intermolecular association effects. The force constants for the S–O bond of the *ortho*-substituted compounds whose S-ring pmr absorbance appears as a singlet are relatively invariant. However, the *o*-methyl compounds studied have significantly lower values for their S–O force constant.

Researches in the Indole Series. XX.[1] Quantum Mechanical Calculations and Charge-Transfer Complexes of Substituted Indoles

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Quantum mechanical as well as charge-transfer complex properties have been determined for a number of indole derivatives. Good agreement has been found between these two ways of evaluating the electron-donor ability. Methyl lysergate does not display exceptional donor ability.

The problem of correlating the "psychotropic" properties of molecules with some of their electronic properties has attracted much interest since the proposition of the "submolecular" hypothesis for the action of these drugs.[2] Chlorpromazine was found to be a very potent donor; Karreman, Isenberg, and Szent-Györgyi[2a] suggested that its tranquilizing activity might be related to an electron-donating action. These papers pointed out the remarkable ability of indole compounds to act as electron donors in the formation of charge-transfer complexes (CTC) with various donors, for instance, flavine mononucleotide (FMN).

The electron-donating ability of a compound can be estimated experimentally from the wavelength of the absorption maximum of the CTC formed with appropriate donors. With a given acceptor these wavelengths are inversely proportional to the ionization

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potential of the donors. The ionization potential is related to the energy of the highest occupied molecular orbital (HOMO). This can be calculated using the simple Hückel LCAO-MO theory. Indoles, however, are better donors than would be expected from their HOMO's.[2,3]

Snyder and Merril[4] carried out molecular orbital (MO) calculations for several series of hallucinogenic drugs and their nonhallucinogenic structural analogs (methoxylated arylethylamines and tryptamines, LSD) and found a correlation between the hallucinogenic potency and the energy of the HOMO's. Interest in the possible role of charge-transfer complexes (CTC) in the biological activity of important indole derivatives has led to investigation of CTC's of indoles with various acceptors such as DNP[5] and chloranil.[6] These results have been found in agreement with the energies of the highest occupied molecular orbitals of various indole derivatives calculated by Green and Malrieu.[7]

5-Methoxy-N,N-dimethyltryptamine is a potent psychotropic agent[8] whereas N,N-dimethyltryptamine itself is less active.[9-11] The influence of 6-hydroxylation on the psychotropic activity of tryptamines is not yet clear.[12] However, a comparison of DMT, 4-OH-DMT, and 5-OH-DMT led to the conclusion[13a] that the important factor would not be so much the hydroxyl group in itself, as its position; methylation of the hydroxyl group of psilocin which does not profoundly influence its electronic properties diminishes the biological activity;[13b] the reverse occurs with bufotenine.

It thus became interesting to investigate the possible ways in which substitution of the indole system might influence biological activity. An obvious way would be electron donation, if electron availability on the indole ring is important in performing biologically important tasks.

The influence of methoxyl substitution on the "neighboring-group participation" of the indole ring in the solvolysis of tryptophyl tosylates has been investigated.[1] In the present study (a) the electronic properties of methoxylated indoles and tryptamines have been calculated using the simple Hückel LCAO-MO theory and (b) their ability to form CTC's with two acceptors, trinitrobenzene (TNB) and tetracyanoethylene (TCNE), have been studied. The choice of methoxy- rather than hydroxy-substituted[14] indoles was one of experimental convenience.

Quantum Mechanical Properties. Methods of Calculation.—The electronic properties of the molecules have been calculated using the simple Hückel LCAO-MO theory. We used Streitwieser's parameters[15] (set 1)

$$\delta_{\ddot{N}} = 1.50 \qquad \eta_{C\ddot{N}} = 0.8$$

$$\delta_{\ddot{O}} = 2.00 \qquad \eta_{C\ddot{O}} = 0.8$$

(where δ and η are respectively, the diagonal and off-diagonal elements).

The methyl and other-alkyl groups were represented by a model which takes into account both their inductive and hyperconjugative effects.

$$\delta_{C_1} = -0.10 \qquad \eta_{CCH_3} = 0.70 \qquad \text{(used for } C_1C_2{\equiv}H_3\text{)}$$

$$\delta_{H_3} = -0.20 \qquad \eta_{C\equiv H_3} = 2.00$$

$$\delta_{\ddot{O}} = 1.90 \qquad \eta_{OCH_3} = 0.55 \qquad \text{(used for } OCH_3\text{)}$$

In the correlations with the absorption maxima of the charge-transfer complexes, we have used the values of the coefficient of the highest occupied molecular orbital, k, which parallel the ionization potentials[15] and the donor ability of the whole molecule. This index is expressed in a conventional (negative) unit, β, which lies around 3.5 ev; the smaller k, the stronger the donor ability. For reasons stated below we have calculated the energies of the HOMO's, both with set I parameters and with set II which differs from set I only by changing $\eta_{C\ddot{O}}$ from 0.80 to 1.00. The values of the energies of the HOMO are listed in Table II.

As a localized index, we use the total net charge[15,16] and the superdelocalizability.[17] For a given atom r this index is equal to

$$S_r = 2\sum_{j,occ} \frac{c_{rj}^2}{k_j}$$

where c_{rj} represents the coefficient of the molecular orbital j on the atom r, and k_j its energy. The summation involves all the molecular orbitals which are occupied in the ground state. This index was derived from the perturbation theory and reflects the stabilization energy of the transition state in an electrophilic reaction on atom r, and thus the ease of such a reaction.

The calculation of σ charges have been performed in the Del Re localized model.[18] For this problem we used the parameters recently proposed by Berthod and Pullman.[19]

Results.—Given in Table I are the net charges (π only and $\sigma + \pi$) and the superdelocalizabilities for indole, tryptamine, and their four methoxy derivatives.

It seems important to take into account the contribution of σ electrons, particularly if they play a role in the electrostatic forces which are, in part, responsible for the linkage in charge-transfer complexes.[20] The superdelocalizabilities should reflect the availability of electrons for chemical reactions on a given

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TABLE I
NET CHARGES AND SUPERDELOCALIZABILITIES IN SUBSTITUTED INDOLES

Compd	C_2 — Q			C_3 — Q			C_4 — Q			C_5 — Q			C_6 — Q			C_7 — Q		
	π	$\sigma+\pi$	S	π	$\sigma+\pi$	S	π	$\sigma+\pi$	S	π	$\sigma+\pi$	S	π	$\sigma+\pi$	S	σ	$\sigma+\pi$	S
Indole	+0.034	+0.085	1.148[a]	−0.122	−0.167	1.238	−0.017	−0.070	1.032	−0.028	−0.081	0.911	−0.020	−0.072	0.966	−0.031	−0.078	0.968
4-MeO-	+0.008	+0.070	1.229	−0.117	−0.164	1.260	+0.036	+0.134	1.012	−0.077	−0.125	1.076	−0.016	−0.066	0.972	−0.065	−0.110	1.128
5-MeO-	+0.024	+0.085	1.144	−0.124	−0.170	1.252	−0.067	−0.114	1.194	+0.017	+0.116	0.898	−0.053	−0.097	1.058	−0.028	−0.073	0.974
6-MeO-	+0.010	+0.071	1.234	−0.121	−0.166	1.258	−0.013	−0.066	1.040	−0.061	−0.106	1.004	+0.027	+0.121	0.948	−0.079	−0.121	1.128
7-MeO-	+0.023	+0.084	1.136	−0.123	−0.168	1.253	−0.052	−0.104	1.192	−0.025	−0.077	0.918	−0.068	−0.112	1.124	+0.019	+0.128	0.952
Tryptamine	−0.008	+0.050	1.298[b]	−0.077	−0.087	1.256	−0.015	−0.069	1.040	−0.029	−0.082	0.908	−0.019	−0.071	0.974	−0.032	−0.079	0.974
4-MeO-	−0.024		1.424	−0.073		1.280	+0.038		1.010	−0.078		1.132	−0.015		0.980	−0.066		1.183
5-MeO-	−0.009		1.300	−0.080		1.273	−0.065		1.254	+0.026		0.888	−0.053		1.089	−0.029		0.981
6-MeO-	−0.023		1.430[c]	−0.076		1.280	−0.011		1.048	−0.062		1.034	−0.028		0.949	−0.080		1.183
7-MeO-	−0.009		1.291	−0.078		1.274	−0.049		1.249	−0.026		0.925	−0.068		1.183	+0.028		0.852

[a] Lit.[22] 1.141. [b] Lit.[22] 1.431. [c] Lit.[22] 1.432. These slight differences are due to the use of different models[15] for the alkyl substituent.

atom; they have been calculated in the usual way considering only π electrons.[15] The inclusion of σ electrons in the calculations could certainly alter the results and, for instance, diminish the superdelocalizability on C_2 with respect to C_3.

It has already been reported for indole itself[21] and for methyl-substituted indoles[7] that the superdelocalizability is higher on C_3 than on C_2. This is true for indoles unsubstituted or dimethyl substituted on C_2 and C_3. In tryptamines substituted in the benzene ring the presence of the alkyl side chain on C_3 reverses the order of the superdelocalizabilities which now become higher on C_2 than on C_3, in agreement with Snyder and Merril[4] (see also ref 22). The superdelocalizability on C_3 is less sensitive to the effect of substituents on the benzene ring than on C_2. On C_4 it is high in the 5- or 7-methoxy derivatives.

The values of the energies of the HOMO will be discussed below. From the calculated charges the *dipole moments* of indole and its methoxy derivatives have been computed: indole, 2.2 D (found 2.05[23]); 4-MeO-, 1.5 D; 5-MeO-, 1.2 D; 6-MeO-, 2.1 D; 7-MeO-, 3.4 D.

Charge-Transfer Complexes. Methods.—Two acceptors have been used: 1,3,5-trinitrobenzene (TNB) in chloroform and tetracyanoethylene (TCNE) in methylene chloride and ethyl acetate. For the various indole derivatives investigated the wavelength of the absorption maximum has been determined. For some donors, the dissociation constants of the charge-transfer complexes have also been determined. For these measurements the donor was used in excess according to Foster and Hanson[24] and when two absorption bands were present the one with the longer wavelength was considered (see below). This widely used spectroscopic method has been criticized by Foster, *et al.*,[25] but it has been used in the present study in order to make possible comparisons with literature values;[24] also its use with a series of closely related donor molecules would lead to values of relative significance.

Discussion. Absorption Wavelength of the CTC's and Ionization Potentials of the Indoles.—The energies of the charge-transfer transitions of a series of donors with the same acceptor are related to the ionization potentials I of the donor molecules by the relation[26]

$$h\nu = I + C$$

where C may be considered constant in the first approximation. Thus one must have the same type of relation between the frequency of the CT transition and the energy of the highest occupied orbital (k)

$$h\nu = k\beta + C$$

The results are summarized in Table II and Figure 1. It appears that the linear relationship between $1/\lambda$ and the calculated ionization potential is reasonably

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TABLE II
CHARGE-TRANSFER BANDS OF INDOLE DERIVATIVES

Compounds	HOMO energy, β Set I	HOMO energy, β Set II	TCNE–CH_3COOEt[c] λ_{max}, mμ	TCNE–CH_3COOEt[c] $10^4/\lambda$	TCNE–CH_2Cl_2 λ_{max}, mμ	TCNE–CH_2Cl_2 $10^4/\lambda$	TNB–$CHCl_3$ λ_{max}, mμ	TNB–$CHCl_3$ $10^4/\lambda$	Ionization potential, eV[f]
Benzene	1.000	1.000	384	26.0	384	26.0	284	35.2	9.25
Anisole	0.754	0.725	470	21.2	509	19.6			8.5–8.20
			368	27.2	387	25.8			
Veratrole	0.616	0.562	550	18.2	592	16.9			
			415	24.0	433	23.0			
Naphthalene	0.618	0.618	505	19.8	555	18.0	365	27.4	8.10
			405	24.6	435	23.0			
Phenanthrene	0.605	0.605	490	20.4	537	18.6	370	27.0	8.02
p-Terphenyl	0.592	0.592			560	17.8			
					375	26.6			
Pyrene	0.445	0.445			724	13.8			7.58
Anthracene	0.414	0.414					460	21.7	7.23
Indole	0.600[a]	0.600	510	19.6	560	17.8	390	25.6	
4-MeO-indole	0.517[b]	0.473	715	14.0	720	13.9	455	22.0	
			510	19.6	527	18.9	370	27.1	
5-MeO-indole	0.598	0.592	610	16.4	625	16.0	420	23.8	
6-MeO-indole	0.528[d]	0.489	680	14.7	720	13.9	[g]		
			550	18.2	570	17.5	375	26.7	
7-MeO-indole	0.552[f]	0.518	660	15.1	670	14.9	450	22.2	
			530	18.8	560	17.8			
Tryptamine	0.549[b]	0.549	500	20.2			370	27.4	
5-MeO-tryptamine	0.545[e]	0.540	615	16.2	630	15.8	430	23.2	
4,5-$(MeO)_2$-indole	0.502	0.465	720	13.9	740	13.5			
Methyl lysergate	0.487	0.487			670[h]	14.9	460	21.7	
					520	19.2			

[a] Lit.[22] 0.5999. [b] Calculated for 5-OH-indole: 0.598; lit.[22] 0.5164 for 5-MeO-indole. [c] Lit.[23] 0.5117 for 5-MeO- and 0.5137 for 5-OH-tryptamine. [d] Calculated for 6-OH-indole: 0.535; lit.[22] 0.4700 for 6-OH-tryptamine. [e] 4-OH-indole: 0.526. [f] 7-OH-indole: 0.558. [g] Long-wavelength band very badly separated from the other one. [h] At −60°. [i] V. I. Vedeneyev, L. V. Gurvich, V. N. Kondrat'yev, V. A. Medvedev, and Y. L. Frankevich, "Bond Energies, Ionization Potentials, and Electron Affinities," Edward Arnold, London, 1966.

satisfied. The dispersion of points is of the same order of magnitude with hydrocarbons where there is no problem of parameters for the heteroatoms. One may only notice that the highest occupied orbital energy of the methoxylated compounds are generally too high; this means that the conjugation of the MeO group was underestimated in set I; matters are improved by substituting $\eta_{C-O} = 1.00$ (set II) for $\eta_{C-O} = 0.8$ (set I).

From the general agreement between calculations and experiment, one may conclude that both the k value and $h\nu$ give a reasonable idea of the ionization

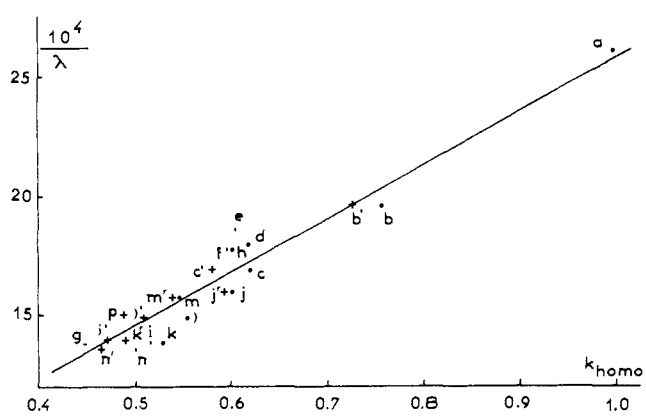

Figure 1.—Charge-transfer complexes of various donors with TCNE in methylene chloride: a, benzene, b, anisole; c, veratrole; d, naphthalene; e, phenanthrene; f, *p*-terphenyl; g, pyrene; h, indole; i, 4-MeO-indole; j, 5-MeO-indole; k, 6-MeO-indole; l, 7-MeO-indole; m, 5-MeO-tryptamine; n, 4,5-$(MeO)_2$-indole; p, methyl lysergate. The primed letters indicate that the calculation of k_{homo} has been made with set II parameters.

potentials of indoles and of their variations with substitutions. One may draw several conclusions. The indoles do not have a very low ionization potential and thus are not very good donors; they lie between naphthalene and anthracene (8.1–7.2 ev). Thus, they do not seem to have the exceptional donor ability (see ref 2) of other pharmacologically important compounds such as phenothiazines. In particular the donor ability of methyl lysergate, which has the same conjugated system as LSD lies between those of 4-MeO- and 5-MeO-indoles. Moreover, the energy of the HOMO of methyl lysergate, as calculated by Streitwieser's parameters, is *0.487*, a value comparable to that of methoxyindoles and very different from the original value of Karreman, *et al.*[24a] (0.218).

It will be seen (Figure 1) that the agreement with the experimental data (λ_{max}) is much better with the new value than with the previous one.

Among the methoxylated indoles the order of decreasing donating ability is as follows.

	4,5-$(MeO)_2$	4-MeO	6-MeO	7-MeO	5-MeO	Indole
Set I	502	517	528	552	598	600
Set II	465	473	489	518	592	600

It can be seen that methoxyl substitution profoundly influences this ability depending on the position of the CH_3O group; whereas 5-methoxylation is practically without effect, 4-methoxylation is very effective in lowering ionization potential by about 1 ev. This does not parallel the observed biological activities.

The influence of the side chain on the position of the absorption maximum is very small, 10 mμ when going

from indole to tryptamine. The representation of the side chain we choose in the calculations tends to overemphasize its effect (see Table I).

Origin of the Second Band.—Some of the indole derivatives give two new bands.[2] When two bands appear in a CT complex the second may arise from the excitation of an electron from the highest occupied orbital of the donor to the second empty orbital of the acceptor, or from the excitation of the (highest − 1) occupied orbital of the donor to the lowest empty orbital of the acceptor. This second case is the most frequent[25c] and has been proposed to explain the position of the second band of the anisole–TCNE complex. Furthermore, with the first mechanism the difference $h\nu_2 - h\nu_1$ would be constant for a given acceptor, which is not found to be the case. On the other hand, consideration of the values of the energies of the highest and (highest − 1) occupied orbitals of the different methoxyindoles (tabulated in Table III), and the differences between the energies of the two CT bands shows clearly the "donor origin" of the second band. In 4- and 6-methoxyindoles the energies of the two highest occupied orbitals are quite different and the two CT bands are well separated. In 7-methoxyindole the two orbitals are a little closer in energy and the bands are closer. In 5-methoxyindole the two orbitals are very close together, and the spectrum shows a large band, which could very well result from the overlap of two bands.

TABLE III

INTERPRETATION OF THE SECOND CT BAND IN METHOXYINDOLES (SET II)

Indole	k_n[a]	k_{n-1}[b]	Δk	$\Delta 10^4/\lambda_{expt}$[c]
4-MeO	0.473	0.807	0.334	5.0
5-MeO	0.593	0.643	0.050	0.0
6-MeO	0.489	0.836	0.347	3.8
7-MeO	0.518	0.749	0.231	2.9
Methyl lysergate	0.487	0.789	0.302	4.3

[a] Energy of the highest occupied orbital (β units). [b] Energy of the (highest − 1) occupied orbital (β units). [c] With TCNE in CH_2Cl_2.

Stability of the Complexes.—In Table IV are reported the values of K measured for 6-indole derivatives with TCNE in methylene chloride. The values for indole itself are very close to Foster's values, obtained in similar conditions. The two wavelengths given in column 2 are the two CT bands.

TABLE IV

ASSOCIATION CONSTANTS

Compd	Temp, °C	λ_{max}, mμ	ϵ_{max}	K, l. mole^{-1}
Indole	4.75	560	2230	4.20[a]
	25		2100	2.75
4-MeO-	6	527	2220	7.34
		720	2780	8.27
5-MeO	6	625	2860	8.45
	25			5.05
6-MeO-	6	570	2440	6.50
		720	2440	7.85
7-MeO-	6	560	2220	8.92
		670	2220	10.81
4,5-$(MeO)_2$-	6	740	1610	17.29

[a] Lit.[24] 4.2 and 2.7.

From these data, the enthalpy variation may be deduced for indole and 5-methoxyindole, using the relation

$$\frac{d \log K}{dT} = -\frac{\Delta H}{RT^2}$$

One finds $\Delta H = -3.1$ kcal/mole for indole and $\Delta H = -4.2$ kcal/mole for 5-methoxyindole. If one assumes that ΔG parallels ΔH in the series, we obtain the following rough result. The indole molecule seems to be less associated than the various methoxyindoles. All of them lie in a narrow range, 7-methoxyindole being the most strongly associated. The dimethoxyindoles would be still more strongly associated. It appears first that there is no direct correlation between K and λ_{max}. This fact seems well established now[20] and shows that the charge transfer does not play a leading role in the stabilization of the ground state of the complex. This stabilization mainly results from electrostatic and Van der Waals forces; the methoxyl group, by increasing the polarizability, will increase the stability.

Numerical values for the hallucinogenic activities of a number of compounds are not yet available, so that detailed correlations seem premature. On the other hand, hydroxy and methoxy substitution lead to very similar electronic properties (footnote *b*, Table II), whereas their influences on physicochemical properties such as membrane permeation are very different.

In particular the lysergic acid molecule does not show the exceptional donor ability it had been attributed and which has aroused so much interest in connection with the exceptional hallucinogenic activity.