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SUBSTITUENT EFFECTS ON ULTRAVIOLET ABSORPTION SPECTRA OF 5-SUBSTITUTED N_b-ACETYL-1-METHOXYTRYPTAMINES STUDIED BY DENSITY FUNCTIONAL THEORY CALCULATIONS#

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Abstract – Density functional theory (DFT) calculations were performed for twelve 5-substituted N_b-acetyl-1-methoxytryptamines (5-X: NO_2, SO_2CH_3, CN, CF_3, Cl, H, CH_3, OH, OCH_3, $NHCOCH_3$, NH_2, $N(CH_3)_2$) in methanol. The respective HOMO→LUMO and HOMO-1→LUMO singly excited configurations are mainly responsible for the lowest and the second singlet excited states (S_1 and S_2). Observed UV absorption spectra of 5-H, 5-NHAc, and 5-CH_3 derivatives are well predicted by simple time-dependent DFT calculations. Distinct substituent effects are found with respect to the energies of MOs responsible for $S_1 \leftarrow S_0$ and $S_2 \leftarrow S_0$ transitions. Both HOMO-1 and HOMO are destabilized by electron-donating groups, and stabilized by electron-withdrawing groups. LUMO+1 of 5-NO_2 derivative should be classified into normal LUMO, which are found for eleven other derivatives as well as indole. Normal LUMO is not significantly affected in energy by electron-donating groups, but stabilized by electron-withdrawing groups.

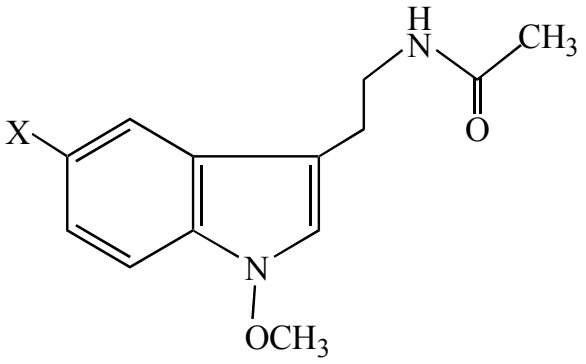
INTRODUCTION

Tryptophan and related compounds play important roles in living cells, and their metabolites should be regarded as biologically active compounds or drugs with various pharmacological actions.[1] They are important in spectroscopic properties of proteins. It is well-known[2] that tryptophan residues in proteins are mainly responsible for near ultraviolet (UV) absorption spectra at wavelengths longer than 250 nm. It has been reported[3] for tryptophan that dual fluorescence spectra derived from $^1L_a \rightarrow {}^1A$ and $^1L_b \rightarrow {}^1A$ fluorescent transitions are especially sensitive to local environments and dynamics in proteins.

#dedicated to Prof. Dr. Ivar Ugi.

In analogy of dual fluorescence spectra of tryptophan, we have recently reported[4] that dual fluorescence excitation and emission spectra resulting from $^1L_a \rightarrow {}^1A$ and $^1L_b \rightarrow {}^1A$ emissive transitions are observed for methanol solutions of 1-hydroxyindoles with various C-C-N_b side-chains such as $CH_2CON(Me)_2$, $CH_2CH_2NHCOOMe$, $CH_2CH(NHAc)COOMe$, and $CH_2CH_2NHCOC(Me)_3$ at 3-position of indole ring. We have demonstrated[4] that dual fluorescence behaviors, elegantly dependent on C-C-N_b side chain, may be useful probe for local environments in proteins. In contrast to the fluorescence behaviors sensitive to C-C-N_b side chain, these 1-hydroxyindoles in methanol exhibit almost the same UV absorption spectra (λ_{max} = 293 and 275 nm). It is reasonable to assume a weak perturbation of C-C-N_b side chain against the spectra. N_b-Acetyl-1-methoxytryptamine in methanol exhibits a very similar UV absorption spectrum (λ_{max} = 290 and 277 nm). The fact strongly indicates that exchange of 1-methoxy group and 1-hydroxy group results in insignificant change in UV absorption spectra.

We happened to notice that N_b-acetyl-1-methoxy-5-nitrotryptamine in methanol exhibits a unique UV absorption spectrum (λ_{max} = 327, 276 and 256 nm), which is quite different from those of 1-hydroxyindoles and 1-methoxytryptamine with C-C-N_b side chain. It is implied that perturbation of nitro group at 5-position of indole ring primarily gives rise to anomalous UV absorption spectrum. It has been demonstrated[5] that the substitution on benzenoid ring affects ^1L_b state qualified as benzene-like in nature, and that the substitution on pyrrole ring affects ^1L_a state qualified as ethylene-like in nature. On the other hand, it is known[6] that UV absorption spectra of indole are much more sensitive to benzenoid substitution than to pyrrole substitution. These facts stimulated us to examine how electronic spectra are affected by 5-substituent on benzenoid ring on the basis of time-dependent density functional theory (TD-DFT) calculations of twelve 5-substituted N_b-acetyl-1-methoxytryptamines. Really obtainable are compounds (**1**, **6**, **8**, and **10**) with NO_2, H, OCH_3, and $NHCOCH_3$ (NHAc) groups, and other compounds (**2**, **3**, **4**, **5**, **7**, **9**, **11**, **12**) with SO_2CH_3, CN, CF_3, Cl, CH_3, OH, NH_2, $N(CH_3)_2$ groups are virtual.



X = **NO_2**, SO_2CH_3, CN, CF_3, Cl, **H**, CH_3, **NHAc**, OH, **OCH_3**, NH_2, $N(CH_3)_2$

Derivative: 1 2 3 4 5 6 7 8 9 10 11 12

The present paper describes that two bonding MOs (HOMO-1 and HOMO) and one anti-bonding MO (LUMO) are mainly responsible for the lowest and the second singlet excited states (S_1 and S_2) of **2**-**12**. Substituent effects on the energies of the MOs were confirmed as follows: Both HOMO-1 and HOMO

are stabilized by electron-withdrawing groups, and destabilized by electron-donating groups. LUMO is not significantly changed in energy by electron-donating groups, but stabilized by electron-withdrawing groups. An extraordinary stabilization of LUMO by NO_2 group may be recognized by the fact that MO with considerable electron density on nitro group becomes LUMO in place of normal LUMO, which is intrinsic to indole and various derivatives.

EXPERIMENTAL AND CONPUTATIONAL METHODS

Both N_b-acetyl-1-methoxy-5-nitrotryptamine (**1**) and N_b-acetyl-1-methoxytryptamine (**6**) were prepared from tryptamine by Somei's method[1]. Oxidizing reagents of N_b-acetyl-2,3-dihydro-5-nitrotryptamine and N_b-acetyl-2,3-dihydrotryptamine yielding 1-hydoxy derivatives are *m*-chloroperbenzoic acid and 30% H_2O_2 in the presence of catalytic amount of sodium tungstate dihydrate ($Na_2WO_4/2H_2O$), respectively. Methylation of these hydroxy derivatives with Me_2SO_4 affords 1-methoxy derivatives (**1** and **6**). Reduction of **1** with $Sn/Ac_2O/AcOH$ generates N_b-acetyl-5-acetylamino-1-methoxytryptamine (**8**)[1d]. Introduction of a methoxy group onto the ring nitrogen of melatonin affords 1-methoxymelatonin (**10**).[7] Purities of these four N_b-acetyl-1-methoxytryptamines (**1**, **6**, **8**, and **10**) were checked by elemental analysis as well as 500 MHz ^{1}H-NMR and mass spectra. Absorption spectra of them in methanol were recorded on a Hitachi U-3210 spectrophotometer. Methanol（Kanto Chemical) for HPLC was used without further purification. Oily compounds (**6**, **8**, and **10)** prevented us from determining reliable molar extinction coefficients as well as molecular structure in X-ray crystallographic analysis.

DFT calculations run by Gaussian 03W[8] program were performed on a work station (Dell Precision 380) with 3.73 GHz Intel Pentium(R) 4 processor extreme edition (2MB L3 cache, 1066MHz FSB). A three-parameter hybrid density functional with a popular polarized double zeta basis set (B3LYP[9]/6-31G(d,p) or 6-31G(d)) was used in the single point energy calculations of geometry-optimized structure in the ground state. For initial input for DFT calculation of **1**, we employed X-ray crystallographic diffraction data[1d] of **1**, which had been obtained by measurements on a Rigaku AFC5R diffractometer with graphite monochromated Cu-$K\alpha$ radiation (λ=154.178 pm). Since crystallographic diffraction data of **6**, **8**, and **10** are not available, we employed initial molecular structures, which had been formed by replacing nitro group with H, NHAc, and OCH_3 groups in the geometry-optimized structure of **1**. B3LYP functional with a diffuse triple zeta basis set (6-311+G(d)) was used in the time-dependent density functional theory (TD-DFT) calculations of geometry-optimized ground state. Polarizable continuum model (PCM) calculations were made to take methanol into account as a solvent. Excitation energies of twenty singlet excited states with oscillator strengths (*f*) and weights of singly excited configurations were evaluated. GaussView W 3.0 was used as an affordable, full-featured graphical user interface for Gaussian 03W.

RESULTS AND DISCUSSION

I. Observed absorption spectra of N_b-acetyl-1-methoxytryptamine and 5-substituted ones.

Figure 1 shows UV absorption spectra of N_b-acetyl-1-methoxytryptamine (**6**) and three 5-substituted ones (**1**, **8**, and **10**) in methanol. These compounds are regarded as methoxy form of 1-hydroxyindoles with C-C-N_b side-chain on pyrrole ring. The former (**6**) exhibits a UV absorption spectrum (λ_{max} = 290, 277, and 223 nm), which is very similar to those (λ_{max} = 292-294, 275, and 222-224 nm)[4] of 1-hydroxyindoles with various C-C-N_b side-chains. TD-DFT calculations predict that exchange between 1-methoxy group and 1-hydroxy group induces insignificant UV spectral change. Observed UV absorption spectrum of **6** is scaled based on assumed molar extinction coefficient of 4700 $M^{-1}cm^{-1}$ (290 nm), which is close to 4730 $M^{-1}cm^{-1}$ (293 nm)[4] of 1-hydroxy-N_b-methoxycarbonyltryptamine.

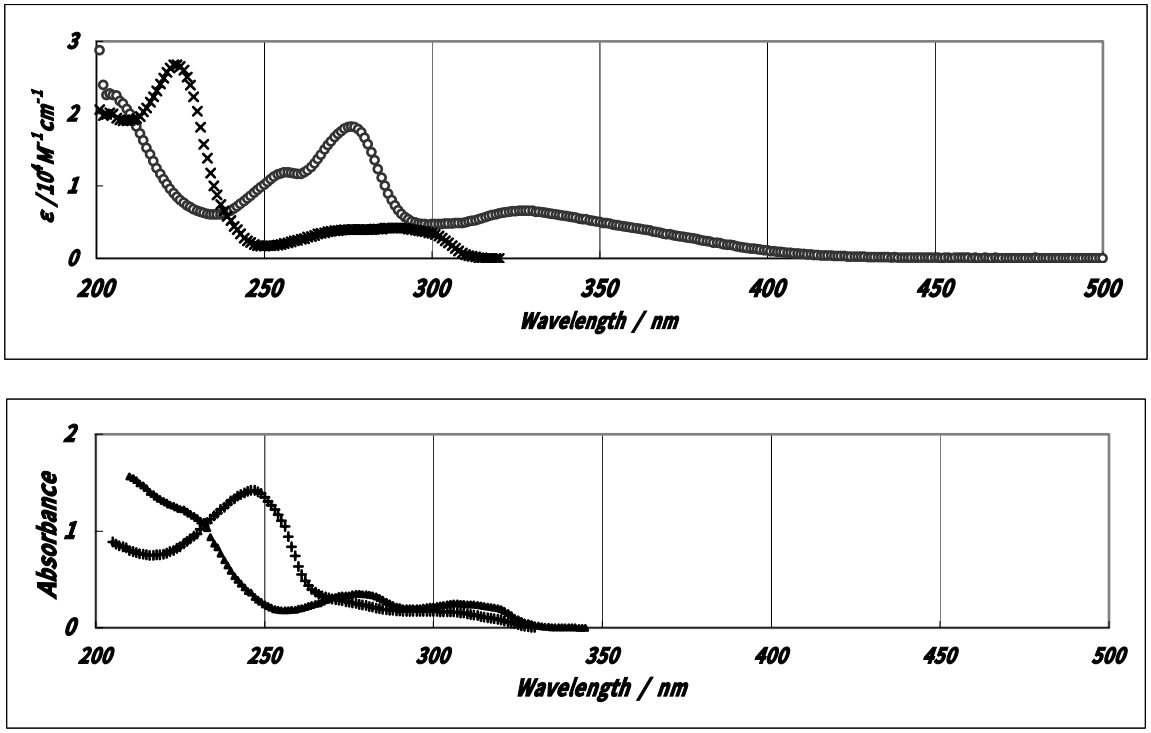


Figure 1. Observed absorption spectra of N_b-acetyl-1-methoxytryptamine and three 5-substituted ones in methanol. Upper: N_b-acetyl-1-methoxy-5-nitorotryptamine, 1 (○) and N_b-acetyl-1-methoxytryptamine, 6 (×). Ordinate is molar extinction coefficient. Lower: N_b-acetyl-5-acetylamino-1-methoxytryptamine, 8 (+) and N_b-acetyl-1, 5-dimethoxytryptamine, 10 (▲) in methanol. Ordinate is absorbance.

UV spectra of 5-NO_2 derivative (**1**) and 5-H prototype (**6**) are quite different from each other. Spectrum (λ_{max} = 327, 276 and 256 nm) of **1** extends over 400 nm. A strong perturbation is suggested for electron-withdrawing NO_2 group on benzenoid moiety. Upon substitution of electron-donating groups, on the other hand, the respective structured band with two peaks (λ_{max} = 307 and 277 nm) and broad one are exhibited by 5-OCH_3 (**10**) and 5-NHAc (**8**) derivatives in the long wavelengths. Longer wavelength peak (307 nm) of **10** is clearly red-shifted compared to that (290 nm) of **6**. The broad long wavelength band of **8** seems to be superimposed with an intense band (λ_{max} = 246 nm), which is remarkably red-shifted compared to the peak (λ_{max} = 223 nm) of **6** and the shoulder peak (λ_{max} = 227 nm) of **10**.

II. Time-dependent DFT calculations of N_b-acetyl-1-methoxytryptamine and 5-substituted ones.

In order to elucidate observed UV absorption spectra, DFT calculations were performed by Gaussian 03W programs[8]. A polarized 6-31G(d) basis set was employed for geometry optimization. The respective DFT and time-dependent DFT (TD-DFT) calculations using a diffuse 6-311+G(d) basis set were performed to calculate energies of optimized structure in the ground state (S_0) and in the excited singlet states (S_n). Figure 2 displays the highest two occupied MOs (HOMO-1 and HOMO) and the lowest two unoccupied MOs (LUMO and LUMO+1) of **1** and **10**. LUMO+1 of **10** is regarded as an anti-bonding MO localized on C-C-N_b side-chain. Similar MO reveals as LUMO+3 for **1**. According to our DFT calculations, HOMO-1, HOMO, and LUMO of **10** are essentially same in surface and nodal plane as those of indole. Comparisons of MOs of **1** and **10** are as follows: HOMO-1 of **1** is almost the same as that of **10**. HOMOs of **1** and **10** are essentially the same with each other. Both anti-bonding LUMO and LUMO+1 of **1** are different from those of **10**. LUMO+1 of **1** corresponds to LUMO of **10**. This is because an MO with high electron density on nitro group is extraordinarily stabilized. Table 1 lists excitation energies, oscillator strengths, and singly excited configurations responsible for each excited singlet states (S_n). Peak wavelengths of the observed UV absorption spectra are also listed.

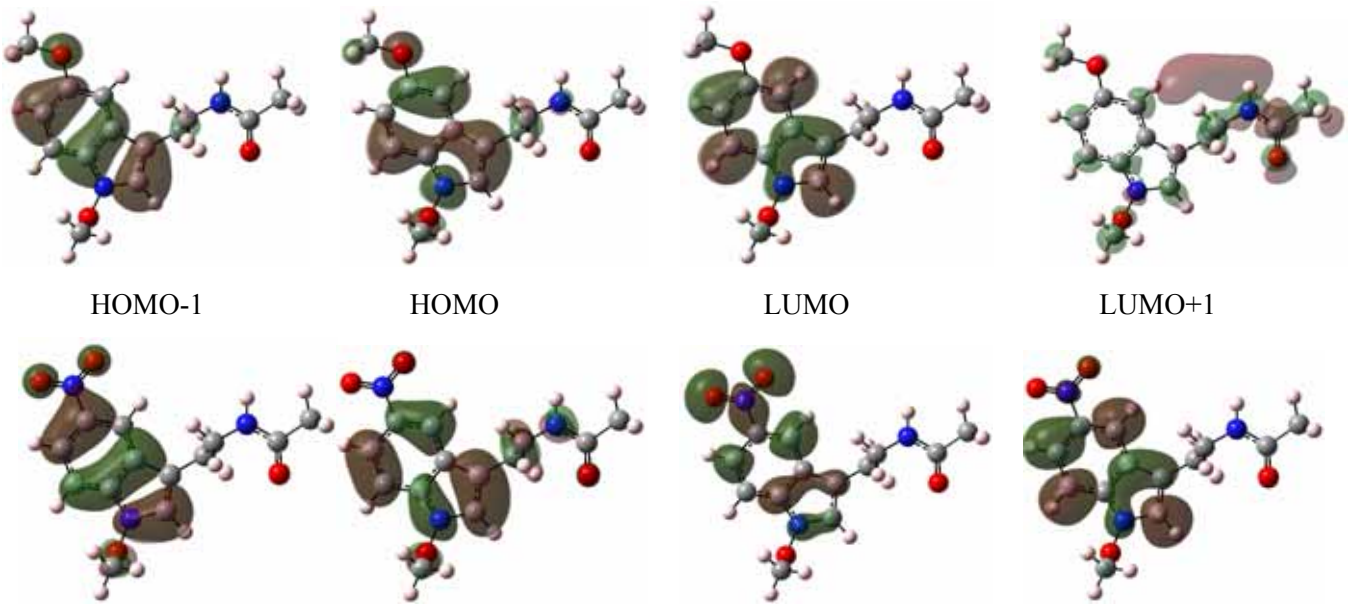


Figure 2. MOs (HOMO-1, HOMO, LUMO, and LUMO+1) associated with singly excited configurations for UV absorption spectra of 10 (upper) and 1 (lower). Colors of atomic balls are gray (C), pink (H), blue (N), and red (O), respectively. Surfaces are depicted with isovalue of 0.020.

Serrano-Andrés and Roos[5] reported a theoretical analysis of the electronic spectrum of indole on the basis of complete active space self-consistent field (CASSCF) method and multiconfigurational second-order perturbation theory (CASPT2). According to their calculations, HOMO→LUMO and HOMO-1→LUMO configurations are attributable to main configurations of ^1L_a and ^1L_b, respectively. We applied these assignments to TD-DFT calculations of 5-substituted N_b-acetyl-1-methoxytryptamines.

Table 1. Excitation energies and oscillator strengths (*f*) of 5-substituted N_b-acetyl-1-methoxytryptamines in methanol obtained by TD-DFT Calculations with B3LYP/6-311+G(d)

X[a] Deriv. #	Excited States	Excitation Energy[b] eV	ν^c /cm^{-1}	λ^d/nm	λ_{obsd}[e]/nm	*f*	Singly Excited Configurations[f]
NO_2	S_1	2.757	22230	449.8		0.0442	H→L(predominant)
1	S_2	3.638	29340	340.8	327	0.2552	-1→L & H→+1
	$S_6(^1L_a)$	4.459	35960	278.1	276	0.2803	H→+1(main); -4→L; -1→L, +1
	S_8	4.720	38070	262.7		0.0253	-4→L & H→+1
	$S_9(^1L_b)$	5.120	41290	242.2	256	0.0754	-1→+1; H→+3, +5
H	$S_1(^1L_a)$	4.346	35050	285.3	290	0.0942	H→L(main); -1→+2
6	$S_2(^1L_b)$	4.752	38330	260.9	277	0.0246	-1→L; H→+2, +3, +4
	S_5	5.440	43880	227.9		0.0844	H→+3, +4, +2
	S_6	5.574	44960	222.4		0.0328	H→+5, +3, +1
	S_7	5.621	45330	220.6	223	0.5993	H→+2, +4, +3, +5, +8; -1→L, +1
NHAc	$S_1(^1L_a)$	4.141	33400	299.4		0.0805	H→L(main); -1→+1
8	$S_2(^1L_b)$	4.388	38770	282.6		0.0011	-1→L; H→+1, L
	S_3	4.907	39580	252.7		0.2636	H→+2, +1, +3; -1→L
	S_4	4.927	39740	251.6	246	0.8310	H→+1, +2; -1→L, +1
OCH_3	$S_1(^1L_a)$	4.096	33030	302.7	307	0.0901	H→L(predominant)
10	$S_2(^1L_b)$	4.575	39030	271.0	277	0.0945	-1→L(main); H→+5, +4
	S_8	5.491	44290	225.8		0.0870	H→+6, +5, +7, +1, +9, +10
	S_9	5.520	44520	224.6		0.2259	H→+7, +5, +6, +4; -1→L, +3
	S_{10}	5.564	44880	222.8		0.2060	H→+7, +5, +8, +4; -1→L
	S_{11}	5.677	45790	218.4		0.0821	H→+8, +4, +9

[a]5-substituent; [b]PCM calculations were performed for methanol as solvent. [c]wavenumber; [d]calculated wavelength; [e]observed peak wavelength; [f]H: HOMO, L: LUMO, -N: HOMO-N, +N: LUMO+N

Since LUMOs of **6**, **8**, and **10** are essentially same as that of indole, they are regarded as normal LUMO. HOMO→LUMO configuration is predominant singly excited configuration for the lowest excited singlet state (S_1) of **10**, and it is main configuration for S_1 of **6** and **8**. Additional configurations are HOMO-1→LUMO+2 for **6** and HOMO-1→LUMO+1 for **8**. Although various HOMO→LUMO+N (N = 0-5) configurations are involved for the second singlet excited state (S_2), the most important configuration is HOMO-1→LUMO configuration. It is thus recognized for **6**, **8**, and **10** that S_1 and S_2 may be regarded as ^1L_a state and ^1L_b state, respectively. The long wavelength bands of **6**, **8**, and **10** have a 290 nm broad peak with a 277 nm shoulder peak, a broad shoulder peak, and explicit twin peaks (λ_{max} = 307 and 277 nm), respectively. The 290 nm broad peak with 277 shoulder peak of **6** may be understood by the oscillator strengths (0.0942 and 0.0246) of S_1 (^1L_a) and S_2 (^1L_b). The broad shoulder peak of **8** may be explained by poor oscillator strength (0.0011) of S_2 (^1L_b) compared to that (0.0805) of S_1 (^1L_a). The twin peaks of **10** are consistent with comparable oscillator strengths (0.0901 and 0.0945) of S_1 (^1L_a) and S_2 (^1L_b). Calculated wavelengths (285.3 & 260.9 nm for **6** and 302.7 & 271.0 nm for **10**) are slightly shorter than observed wavelengths (290 & 277 nm for **6** and 307 & 277 nm for **10**).

Abnormal anti-bonding MOs are responsible for anomalous absorption spectrum of **1** with 5-NO_2 group with a strong perturbing ability, as has been described. Assignments of UV absorption spectrum of **1** should be as follows: The S_6 state mainly derived from HOMO→LUMO+1 configuration may be ascribed to ^1L_a state. Calculated wavelength (278.1 nm) is very close to observed one (276 nm). The S_9

state partly derived from HOMO-1→LUMO+1 configuration may be ascribed to ^1L_b state. Calculated wavelength (242.2 nm) is considerably shorter than observed one (256 nm). It is noteworthy that both ^1L_a and ^1L_b absorption bands exhibit a blue-shift upon the substitution of nitro group. The longest absorption band (λ_{max} = 327 nm) of the observed absorption spectrum shown in Figure 1 should be S_2 derived from HOMO-1→LUMO and HOMO→LUMO+1configurations. Calculated wavelength (340.8 nm) of S_2 is significantly longer than observed one (327 nm). It is highly probable that a weak band of S_1 reflecting HOMO→LUMO configuration is hidden in the tail of the band (λ_{max} = 327 nm).

TD-DFT calculations were performed for eight virtual 5-substituted N_b-acetyl-1-methoxytryptamines (**2**-**5**, **7**, **9**, **11**, and **12**), although the lack of observed absorption spectra prevented us from comparing experimental and theoretical results. Table 2 summarizes excitation energies, oscillator strengths, and singly excited configurations responsible for S_n. We have already demonstrated for real derivatives (**6**, **8**, and **10)** that HOMO→LUMO and HOMO-1→LUMO configurations are attributable to main configurations of ^1L_a and ^1L_b, respectively. Similar assignments are reasonable for virtual derivatives.

Table 2. Excitation energies and oscillator strengths of 5-substituted N_b-acetyl-1-methoxytryptamines (not synthesized) in the lower singlet excited states obtained by TD-DFT calculation with B3LYP/6-311+G(d)

X[a] Deriv. #	Excited States	Excitation Energy[b] eV	ν^c / cm^{-1}	λ^d/ nm	Oscillator Strength, *f*	Singly Excited Configurations[e]
SO_2CH_3	S_1	4.134	33330	300.0	0.0422	H→L(main) & -1→+1
2	S_2	4.521	36470	274.2	0.0139	H→+1 & -1→L
CN	S_1	4.012	32350	309.1	0.0542	H→L(main) & -1→+1
3	S_2	4.387	35390	282.6	0.0018	H→+1 & -1→L
CF_3	S_1	4.279	34510	289.8	0.0593	H→L(main) & -1→+1
4	S_2	4.627	37320	268.0	0.0046	H→+1 & -1→L
Cl	S_1	4.241	34200	292.4	0.0702	H→L(main) & -1→+1
5	S_2	4.611	37190	268.9	0.0294	-1→L & H→+1
CH_3	S_1	4.332	34940	286.2	0.0891	H→L(main) & -1→+2, -1→L
7	S_2	4.673	37690	265.3	0.0344	-1→L(main); H→+2, +3, +1, L
OH	S_1	4.131	33320	300.1	0.0884	H→L(predominant)
9	S_2	4.571	36870	271.2	0.1058	-1→L(main); H→+5, +4
NH_2	S_1	3.943	31800	314.5	0.0808	H→L(predominant)
11	S_2	4.484	36170	276.5	0.0856	-1→L(main); H→+5, +4
$N(CH_3)_2$	S_1	3.783	30520	327.7	0.0852	H→L(main) & -1→+5
12	S_3	4.474	36080	277.2	0.1014	-1→L(main); H→+5, +1

[a]5-substituent; [b]PCM correction; [c]wavenumber; [d]wavelength; [e]H: HOMO, L: LUMO, -N: HOMO-N, +N: LUMO+N

In addition to main HOMO→LUMO configuration, HOMO-1→LUMO+1 configuration slightly contributes to S_1 of derivatives (**2**, **3**, **4**, and **5**) with electron-withdrawing groups such as 5-SO_2CH_3, 5-CN, 5-CF_3, and 5-Cl. It should be noticed that HOMO-1→LUMO and HOMO→LUMO+1 configurations comparably contribute to S_2, respectively. On the other hand, configurations responsible for S_1 and S_2 of derivatives with electron-donating group seem to depend upon electron-donating ability. For derivative (**7**) with weak electron-donating 5-CH_3, many additional configurations are responsible

for S_1 and S_2. Such facts resemble with the results for **6** listed in Table 1. For derivatives (**9** and **11**) with strong electron-donating groups such as 5-OH and 5-NH_2, HOMO→LUMO configuration is predominant for S_1. Both HOMO→LUMO+5 and HOMO→LUMO+4 configurations should be added to the main HOMO-1→LUMO configuration for S_2. The facts are analogous to the results for 5-OCH_3 derivative (**10**). For derivative (**12**) with strongly electron-donating 5-$N(CH_3)_2$, however, HOMO-1→LUMO+5 configuration slightly contributes to S_1. It is remarkable that ^1L_b state derived mainly from HOMO-1→LUMO configuration is not S_2 but S_3 for **12**.

III. Substituent effects on bonding MOs of 5-substituted *N*$_b$-acetyl-1-methoxytryptamines.

MOs of geometry-optimized 5-substituted *N*$_b$-acetyl-1-methoxytryptamines (**1**-**12**) in methanol were determined by DFT calculations with B3LYP/6-311+G(d) followed by PCM corrections. Almost the same spatial surfaces and nodal planes are exhibited by HOMOs of **1**-**12**. It also holds for both HOMO-1 and HOMO-2. These results led us to examine the substituent effect on the energies of these bonding MOs. Energies of occupied MOs can be determined by photoelectron spectroscopy. The UV photoelectron spectra of indole[10] and *l*-tryptophan[11] have been measured with He(I) resonance line. Observed two peaks of *l*-tryptophan at 8.1 and 9.7 eV were interpreted as the combination of the spectra of indole and alanine. No photoelectron spectrum has been reported for 1-methoxyindole derivatives. Based on the photoelectron spectra of *para*-substituted dimethylanilines, nitrobenzenes, acetophenones, and nitrsobenzenes, Egdell et al.[12] have reported the correlations of ionization energy with π-electron density and Hammett σ_p constant. From comparison of photoelectron spectra of mono-substituted and parent acenes, Klasinc et al.[13] have confirmed that electron-donating substituents destabilize and electron-withdrawing substituents stabilize both HOMO and HOMO-1 of parent molecules. They reported good correlations between the lowest ionization potential and Hammett σ_p-value. For twelve 5-substituted *N*$_b$-acetyl-1-methoxytryptamines, we examined the substituent effects on MO energies. Employed Hammett σ_p constants[14] are 0.78 (NO_2), 0.68 (SO_2CH_3), 0.66 (CN), 0.54 (CF_3), 0.23 (Cl), 0.00 (NHAc), -0.17 (CH_3), -0.27 (OCH_3), -0.37 (OH), -0.66 (NH_2), and -0.83 ($N(CH_3)_2$). Figure 3 shows the plots of energies of HOMO, HOMO-1, and HOMO-2 against derivative number (**1**-**12**). Numbering is made by the order that the energy of HOMO increases with increasing number. Energy of HOMO-2 is almost invariant throughout the derivatives. The fact is consistent with poor electron density on indole ring for HOMO-2. Energies of HOMO and HOMO-1 are distinctly dependent on 5-substituents. Compared to the HOMO and HOMO-1 of 5-H prototype (**6**), it is obvious that both HOMO and HOMO-1 are stabilized by electron-withdrawing groups such as NO_2 (**1**), SO_2CH_3 (**2**), CN (**3**), CF_3 (**4**), and Cl (**5**), and that they are destabilized by electron-donating groups such as CH_3 (**7**), OH (**9**), OCH_3 (**10**), NH_2 (**11**), and $N(CH_3)_2$ (**12**). Only an exception is shown by 5-NHAc derivative (**8**), the σ_p-value of which is zero. HOMO is slightly destabilized, and HOMO-1 is significantly destabilized by 5-NHAc.

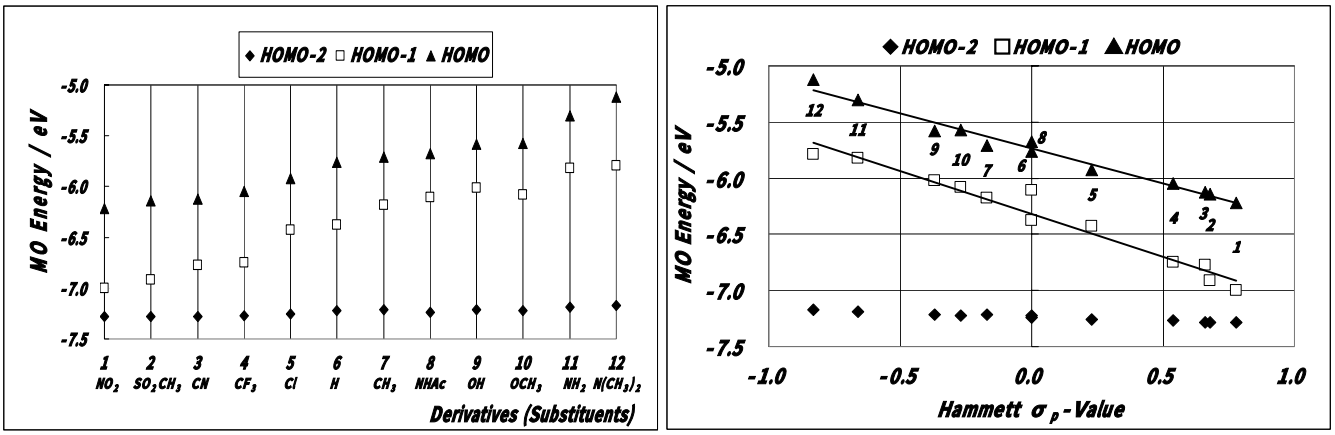


Figure 3. Plots of calculated energies of bonding MOs (HOMO, HOMO-1, and HOMO-2) against derivative number (left figure) and Hammett σ_p constant (right figure) of substituents for twelve 5-substituted N_b-acetyl-1-methoxytryptamines.

Also shown in Figure 3 are the plots of the energies of HOMO, HOMO-1, and HOMO-2 against the Hammett constant (σ_p). Energies of HOMO and HOMO-1 correlate linearly with σ_p-values. Correlation coefficients of the plots for HOMO and HOMO-1 are -0.99 and -0.98, respectively. Slope (-0.63 eV) of the plot for HOMO is slightly less than that (-0.77 eV) of the plot for HOMO-1. It has been demonstrated[5] that the respective substitutions on benzenoid and pyrrole rings affect ^1L_b and ^1L_a states. Significant 5-substituent effects are thus expected for bonding MOs which are responsible for excited configurations of ^1L_b. Mainly responsible for the ^1L_b states of **6-12** is HOMO-1→LUMO excited configuration, as shown in Tables 1 and 2. The HOMO-1→LUMO configuration is secondly responsible for those of **2-4**. (HOMO→LUMO+1 excited configuration is mainly responsible for ^1L_b states of **2-4**.) π-electrons delocalize over both benzenoid and pyrrole rings. These facts might rationalize that not only HOMO-1 but also HOMO are affected in energy by 5-substituents (benzenoid substitution).

It is known for a long time that electron density correlates with σ_p-value.[15] On the basis of CNDO/2 MO method calculations of substituted pyridines, Pilarski et al.[16] have reported that π-electron density of pyridine ring correlates well with various electronic substitution constants. Namely, ring π-electron densities of pyridines with electron-donating substituents are higher than those of pyridines with electron-withdrawing substituents. For 5-substituted N_b-acetyl-1-methoxytryptamines in the present study, squares of coefficients (c_i^2) of all the P_z-type basis functions were counted for ring atoms, the coordinates of which were made lying on the x-y plane in the standard orientation. Nevertheless corrections derived from other basis functions (P_x, P_y, S, D) were not made, Σc_i^2-values may reflect π-electron density in a rough approximation. Table 3 summarizes the energies of HOMO-2, HOMO-1, and HOMO of twelve 5-substituted N_b-acetyl-1-methoxytryptamines as well as HOMO's Σc_i^2-values for six carbon atoms of benzenoid ring. Figure 4 shows that HOMO energy increases with increasing Σc_i^2-values. The fact implies that screening of nucleus charge by π-electrons results in lowering

ionization potential of HOMO. Consequently, HOMO is destabilized (stabilized) by electron-donating (electron- withdrawing) substituents.

Table 3. HOMO's Σc_i^2-values of P_z-type basis functions of carbon atoms in benzenoid ring for twelve 5-substituted N_b-acetyl-1-methoxytryptamines in methanol. Also listed are energies of higher bonding MOs (HOMO-2, HOMO-1, and HOMO) of twelve derivatives.

Deriv.	X	HOMO-2 / eV	HOMO-1 / eV	HOMO / eV	Σc_i^2 (HOMO) *benzenoid*
1	NO_2	-7.28	-6.99	-6.23	0.163
2	SO_2CH_3	-7.28	-6.91	-6.15	0.167
3	CN	-7.28	-6.77	-6.12	0.155
4	CF_3	-7.27	-6.75	-6.04	0.171
5	Cl	-7.25	-6.42	-5.93	0.177
6	H	-7.22	-6.36	-5.77	0.179
7	CH_3	-7.21	-6.17	-5.71	0.186
8	NHAc	-7.24	-6.09	-5.68	0.203
9	OH	-7.21	-6.01	-5.58	0.196
10	OCH_3	-7.22	-6.09	-5.57	0.208
11	NH_2	-7.19	-5.82	-5.30	0.244
12	$N(CH_3)_2$	-7.17	-5.79	-5.11	0.216

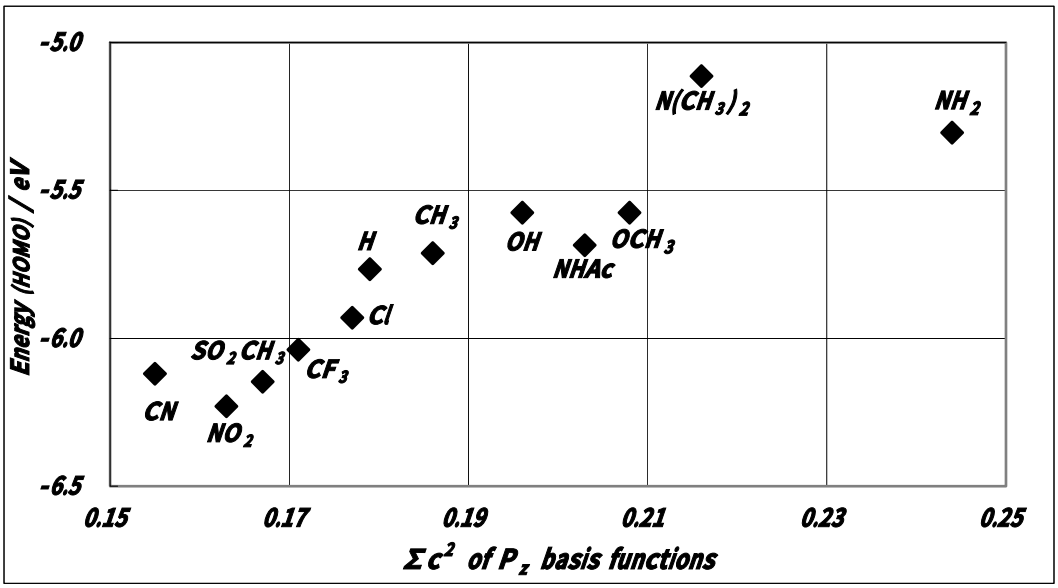


Figure 4. Correlations between HOMO energy and sum total of squares of coefficients (Σc_i^2) for all P_z ($2P_z$, $3P_z$, $4P_z$, and $5P_z$) basis functions. All the c_i^2-values of P_z basis functions on six carbon atoms in benzenoid ring are counted.

IV. **Substituent effects on anti-bonding MOs of 5-substituted N_b-acetyl-1-methoxytryptamines.**

As is distinct from the same order in energy of HOMO, HOMO-1, and HOMO-2 for each derivative, the order of the energy of anti-bonding MOs (LUMO+N, N=0, 1, …) varies from derivative to derivative. LUMO+1 of **1** corresponds to LUMO of **2-12,** as has been described. These MOs are classified into the first group. LUMOs of **3**, **6**, and **11** as well as LUMO+1 of **1** are displayed at the upper part of Figure 5. Based upon the similarity of spatial surfaces and nodal planes, (LUMO+3 of **1**), (LUMO+1 of **2-5** and **8**),

(LUMO+2 of **6** and **7**), and (LUMO+5 of **9**-**12**) may be classified into the second group. LUMO+3 of **1**, LUMO+1 of **3**, LUMO+2 of **6**, and LUMO+5 of **11** are displayed at the lower part of Figure 5.

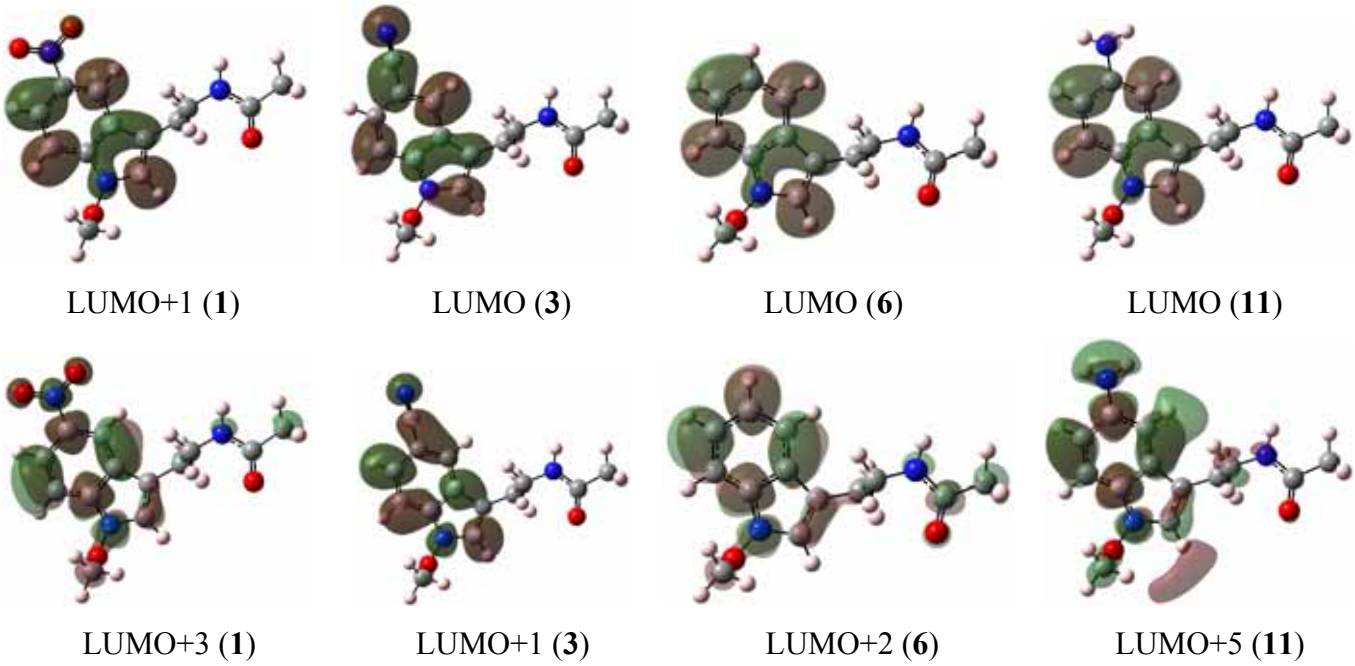


Figure 5. Anti-bonding MOs responsible for the long wavelength absorption bands of 1, 3, 6, and 11. Those localized on indole ring are classified into the first and the second groups on the basis of MO surface and nodal planes. Upper: the first group, Lower: the second group. Surfaces are depicted with isovalue of 0.020. Colors of atomic balls are gray (C), pink (H), blue (N), and red (O), respectively.

Anti-bonding MO localized on side-chain reveals as LUMO+2 of **1**-**5** and **8** or LUMO+1 of **6**, **7** and **9**-**12**. LUMO+1 of **10** is displayed in Figure 2. Such MOs are classified into the third group. Energies of anti-bonding MOs belonging to the first, the second, and the third groups are plotted against Hammett σ_p-constant in Figure 6.

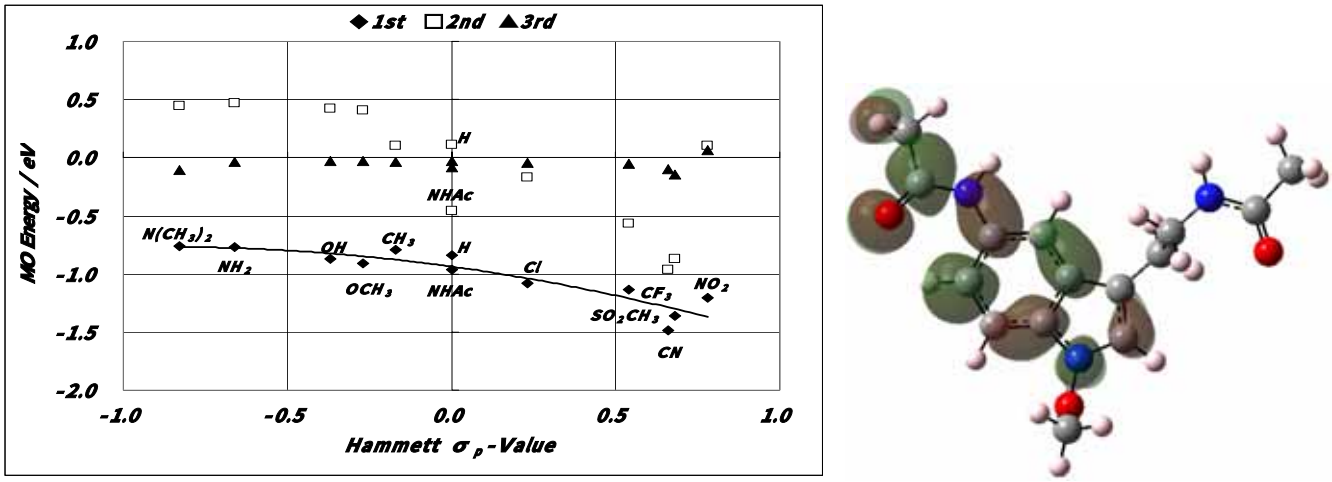


Figure 6. Energies of anti-bonding MOs classified into the first, the second, and the third groups are plotted against Hammett σ_p-value. Depicted surfaces for LUMO+1 of 5-NHAc-derivative (8) are also displayed. Isovalue for MO surface: 0.020

Anti-bonding MOs of the third group are curious ones with poor electron density on indole ring. Almost no substituent effect on the MO energy is consistent with the poor ring electron density. In contrast to

this, energy of the first group MO definitely decreases with increasing σ_p-value in the positive region. It is little affected by σ_p-value in the negative region, although it seems to decrease gradually with increasing σ_p-value according to a fitting curve. It is thus concluded that MOs belonging to the first group are stabilized by electron-withdrawing groups. Similar behaviors are observed with respect to the second group MOs. Significant stabilization is caused by electron-withdrawing groups such as SO_2CH_3, CN, and CF_3. Noticeable is considerable destabilization by electron-donating groups such as OH, OCH_3, NH_2, and $N(CH_3)_2$. Consequently, energies of the second group MOs are higher than those of the third group MOs in the negative σ_p region. It should be noted that LUMO+1 of 5-NHAc derivative (**8**) is anomalously stabilized. It is remarkable that MO surface spreads over 5-NHAc group, as displayed in Figure 6.

The longest wavelength band of UV absorption spectra of 5-substituted *N*$_b$-acetyl-1-methoxytryptamines in methanol may be successfully predicted by simple TD-DFT calculations. Because of negligible perturbation of C-C-*N*$_b$ side chain at 3-position of indole ring, UV absorption spectra of 5-substituted 1-methoxyindoles were actually studied. A strong perturbation of NO_2 group gives rise to a substantially stabilized LUMO with significant electron density on NO_2 group, and 5-NO_2 derivative (**1**) is non-fluorescent as is distinct from non-fluorescent behavior of **2**-**12**. The LUMO of **1** is quite different from normal LUMO being intrinsic to indole and various derivatives. With the exception of 5-NO_2 derivative (**1**), distinct substituent effects can be predicted for the energies of MOs (HOMO-1, HOMO, and LUMO), which are associated with the single excited configurations for the lowest and the second singlet excited states (S_1 and S_2). The energies of MOs (HOMO-1, HOMO, and LUMO) correlate well with electron-withdrawing (electron-donating) ability of 5-substituents. Information about the energies of the MOs is very important not only for understanding UV absorption and photoelectron spectra but also for predicting reactivity. Molecular designs by selecting appropriate substituent may be expected to adjust MO energies suitable for various nucleophilic and electrophilic reactions of 1-methoxyindoles, which must be important for biologically active compounds with pharmacological actions.

The present TD-DFT calculations predicted that the substitution of electron-withdrawing groups except for NO_2 at 5-position of indole ring results in stabilizations of HOMO-1, HOMO, LUMO, and LUMO+1. We could not synthesize 5-substituted *N*$_b$-acetyl-1-methoxytryptamines with electron-withdrawing substituents such as SO_2CH_3, CN, CF_3, and Cl. Unfortunately, such a circumstance prevented us from examining observed UV absorption spectra by TD-DFT calculations.

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