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Experimental and theoretical ultraviolet spectra of haloindoles

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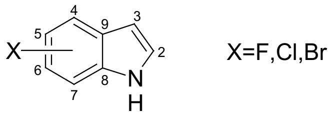
Abstract—The UV spectra of indole and the 4-, 5-, 6-, and 7-haloindoles ($X = F$, Cl, Br) have been recorded in methanol and calculated using time-dependent density functional theory. The lowest-energy UV absorption of each of the indoles is due to the HOMO–LUMO π–π^* transition. This transition shifts to the red for the haloindoles relative to indole mainly as a result of the destabilization of the haloindole HOMOs.

The vast array of naturally occurring organohalogens includes a variety of haloindoles, predominantly of marine origin.[1] Regioisomeric halotryptophans have received attention as constituents of pharmacologically active peptides produced by lower marine animals[2] and as agents that inhibit polymerization of hemoglobin in sickle cell anemia.[3] Some haloindoles have gained importance as synthetic intermediates for compounds of pharmaceutical interest.[4] One of the most widely used synthetic haloindole derivatives is 5-bromo-4-chloro-3-indoyl-β-D-galactoside, commonly known as X-gal; this chromogenic substrate is used to screen for DNA plasmids inserted into the β-galactosidase marker gene (blue-white screening).[5]

It is well known that the aromatic indole system gives rise to absorbance bands in the near UV. Although the UV spectra of various substituted indoles have been determined[6–11] and calculated[11,12] with energetic accuracy previously, we are interested in understanding the absorption trends of these series of spectra, and have therefore determined and calculated the UV spectra systematically for the 4-, 5-, 6-, and 7-fluoro-, chloro-, and bromo-indoles.



The lowest energy UV absorption of indole and its substituted analogues is the HOMO–LUMO π–π^* transition,[6,7] a band sensitive to increased benzenoid substitution and solvent dielectric constants, among other factors.[6,11] The UV spectra of indole and the 4-, 5-, 6-, and 7-haloindoles were recorded in methanol (Fig. 1).[13] In accord with previous studies,[6–10] the absorptions of indole occur at higher energies than do those of its halogenated analogues. The wavelengths of the HOMO–LUMO transitions of each indole are reported in Table 1. Overall, the energies of the HOMO–LUMO absorptions increase slightly in the order: bromo-indole < chloro- < fluoro- < parent indole. Additionally, the HOMO–LUMO absorption of the 5-haloisomer is the most red shifted, regardless of the halogen substituent. The energies of the HOMO–LUMO transitions for the chloro- and bromo-isomers increase from the 5-isomer < 6- < 7- < 4-.

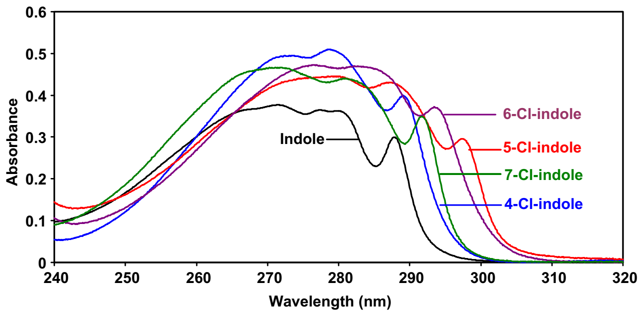


Figure 1. Absorbance spectra of indole and chloro-indole regioisomers in methanol at 6.4e −4 M of indole and at 7.9e −5 M of each of the chloro-indoles.

Keywords: Haloindoles; UV spectroscopy; TDDFT.

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Table 1. HOMO–LUMO transitions of 4-, 5-, 6-, and 7-haloindoles

	X = H (nm)		X = F (nm)		X = Cl (nm)		X = Br (nm)	
	Expt.	Calcd	Expt.[a]	Calcd[b]	Expt.[c]	Calcd[b]	Expt.[c]	Calcd.[b]
4-X	287.9,[c] 288.2[e]	263.3[b], 279.9[d]	284.5	259.4	289.1	268.3	289.5	270.6
5-X			295.5, 295.0[c]	268.5	297.4	270.6	297.3, 297.6[e]	272.4
6-X			282.0[c]	267.0	293.5	270.6	293.8	272.3
7-X			285, 284.8[c]	258.6	291.7	266.5	292.3	268.3

[a] Ref. 10.

[b] This work, TDDFT-calculated at B3LYP/6-311+G*//B3LYP/6-31G* in the gas phase.

[c] This work, in methanol.

[d] Ref. 12, using CASSCF/CASPT2 in the gas phase.

[e] Ref. 7, in ethanol.

The absorption and emission spectra of indole have been recently calculated in the gas phase and in solution using CASSCF and CASPT2 methods, and were comparable to experimental values.[12] Because our goal was to understand better the ranking of the HOMO–LUMO absorption energies among each series of fluoro-, chloro-, and bromo-indole isomers, we chose to minimize computational cost by using time-dependent density functional theory (TDDFT) to calculate the UV spectra of indole and its monohalogenated analogues in the gas phase at B3LYP/6-311+G*//B3LYP/6-31G*.[14,15]

Our calculations confirm that the HOMO–LUMO absorptions are all π–π^* transitions; Figure 2 depicts each HOMO and LUMO for indole and its chlorinated isomers. The trend in HOMO–LUMO transition energies among each family of haloisomers is consistent, increasing in energy in the order: 5- < 6- < 4- < 7-haloindole (Table 1). The wavelengths of these calculated transitions are an average of 20–25 nm lower than the solution-phase experimental values. This discrepancy can be attributed at least in part to solvent effects,[6,11,12,16] or to the use of TDDFT, as more accurate transition energies are obtained by using multiconfigurational methods to model the excited states.[12,17]

The red shift of the HOMO–LUMO absorption in the haloindoles versus indole itself can be accounted for by

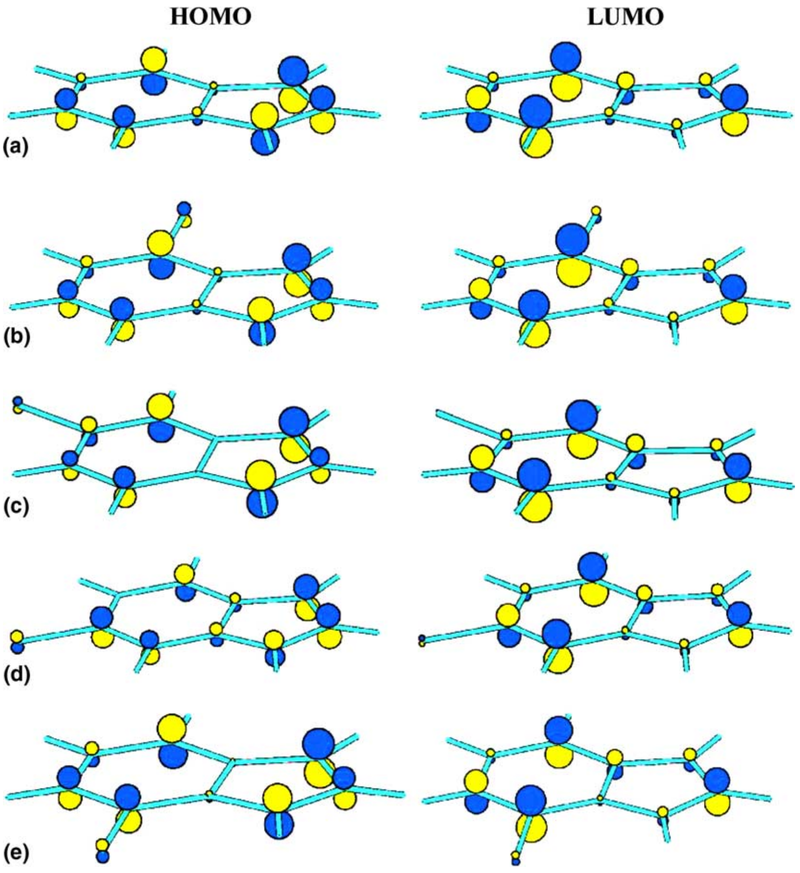

Figure 2. The HOMO and LUMO of each of (a) indole, and (b) 4-, (c) 5-, (d) 6-, and (e) 7-chloro-indoles, all calculated at B3LYP/6-311+G*//B3LYP/6-31G*.

comparing their HOMOs. The haloindole HOMOs ($HOMO_X$) have antibonding interactions at the C–X bond. These effects are depicted by the chloro-indole HOMOs in Figure 2. These interactions destabilize $HOMO_X$ in the ground state relative to the indole HOMO ($HOMO_H$). Another factor that contributes to the destabilization of $HOMO_X$ is the disruption of the C_5–C_4–C_9–C_8–N continuous bonding interaction present in $HOMO_H$ and the HOMO of 4-haloindole ($HOMO_4$). $HOMO_5$ and $HOMO_7$ have little or no electron density at the C_8–C_9 bond; $HOMO_6$ lacks electron density on C_5.

A comparison of the HOMOs and LUMOs of the haloindoles allows us to measure the stabilities of these orbitals relative to each other. While there are small variations among the electron densities on individual atoms of the haloindole HOMOs, the main difference stems from the continuous bonding electron density (or lack thereof) along the path C_5–C_4–C_9–C_8–N. It is by examining this path that we can rank the $HOMO_X$ in terms of energy, increasing in the order: 4- < 6- < 7- < 5-. Upon inspection, the LUMOs of the haloindoles are similar except for the degree of antibonding interaction in the C–X bond. Thus, by examination of the C–X bond in $LUMO_X$, the energies of these orbitals increase in the order: 5- < 6- < 7-≈4-.

The instability of $HOMO_5$ and stability of $LUMO_5$ account for the fact that, experimentally and computationally, the lowest energy HOMO–LUMO transition belongs to the 5-haloisomer. $HOMO_5$ is destabilized in comparison to the other $HOMO_X$ due to the absence of bonding electron density across the C_8–C_9 bond, as represented by 5-chloro-indole in Figure 1c. Coupled with this is the stability of $LUMO_5$ relative to the other LUMOs: the absence of electron density on the halogen averts the destabilizing antibonding interaction of the C_5–X bond.

The trends of the calculated energies for the HOMO–LUMO transitions are, in increasing order: 5- < 6- < 4- < 7-haloindole, whereas the energies of the experimental HOMO–LUMO transitions are: 5- < 6- < 7- < 4-haloindole. It is not immediately clear why the 7-haloindoles are calculated to have a HOMO–LUMO absorption higher in energy than the 4-derivative. The orbitals of these regioisomers show $HOMO_4$ to be apparently more stabilized than $HOMO_7$, and $LUMO_4$ and $LUMO_7$ to be similar in energy. Thus, the difference between $HOMO_4$ and $HOMO_7$ would predict a higher-energy absorption for the 4-isomer versus the 7-, as is observed experimentally. This discrepancy between the experimental and calculated results may due to a variation in solvent effect on the molecular dipoles of the haloisomers in solution.

The solution-phase UV spectra of the 4-, 5-, 6-, and 7-haloindoles in methanol correlate well with those recorded previously.[6–9,12] The trends of the lowest energy HOMO–LUMO π–π^* transitions of these isomers are also predicted well by theory, particularly for the 5- and 6-haloisomers. The difference between the experimental and calculated energy trends for the 4- and 7-haloisomers may be due to differing stabilization of the two molecular dipoles in solution.

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