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PHOTOCYCLIZATION OF N-CHLOROACETYL DERIVATIVES OF INDOLYLETHYLAMINES TO AZEPINOINDOLES AND AZOCINOINDOLES. CORRELATION OF THE REACTIVITY OF INDOLE RADICALS WITH FRONTIER ELECTRON DENSITIES CALCULATED BY UNRESTRICTED HARTREE-FOCK MO

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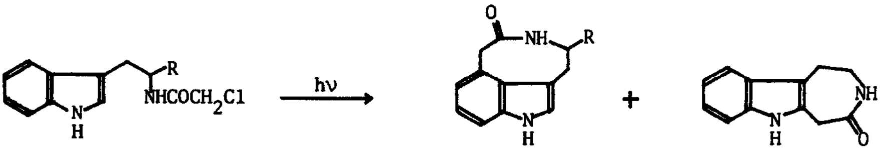
Several years ago we reported the synthesis of azocinoindole derivatives (ii) from N-chloroacetyltryptophan (i)[1,2] through a new type of photocyclization which has been extended to derivatives of aromatic amino acids and pharmacodynamic amines to afford many novel heterocycles.[3] On the basis of studies on fluorescence quenching,[4] solvent effects[5] and flash photolysis,[6] a common feature in the initial stages of the photocyclizations in aqueous solvents has been proposed.[7] Intramolecular electron transfer (photoionization) from the excited singlet state of an aromatic chromophore to the chloroacetyl moiety, probably *via.* an exciplex, leads to the cleavage of the C-Cl bond. The resultant methylene radical couples readily with the aromatic radical cation to form cyclization products. The reactivity of the position on the aromatic ring to which the methylene radical couples may correspond to the odd electron density.



i: R=CO_2H
3: R=H

ii: R=CO_2H
13: R=H

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There are many reports on radical reactions of aromatic[8] and symmetrical heteroaromatic compounds,[9] whose reactivities correlate well with MO data, while similar correlations for heterocycles without symmetry, such as thiazole,[10] quinoline and isoquinoline,[11] are missing. Likewise, there are no reports correlating radical reactivities of indoles with MO calculations.

We have now examined photocyclizations of N-chloroacetyl derivatives of seven isomeric indolylethylamines trying to correlate the reactivities at various positions of indole with MO calculation.[12] On irradiation with a low-pressure mercury lamp (2537Å) in 50% aqueous ethanol containing $NaHCO_3$, N-chloroacetylaminoethylindoles (1-7) gave azepinoindoles (8,11,12,16,17,18, 21) and azocinoindoles (9,13,14) through photocyclizations at *ortho* and *peri* positions. Quantum yields[14] as determined using a ferrioxalate actinometer[15] are recorded in Table I. Positions 3, 4 and 6 have a high reactivity, whereas positions 1, 2 and 5 are less reactive, in particular, no cyclization products at position 1 were detected.[16]

Table I. Quantum Yields (Φ) in the Photocyclization of 1-7.

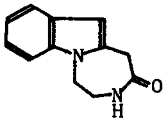
Starting material					Product			
			mp°C	Φ[c]			mp°C	Φ[e]
1	(1)[a]	–[b]	81-82	.233	8	(2)[d]	253-254	.062
					9	(7)	254-255	.108
2	(2)	H	143-145	.253	10	(1)		.0
					11	(3)	230-232	.250
3[17]	(3)	H		.230	12	(2)	245-247	.025
					13	(4)	290-292	.150
4	(4)	H	106-108	.277	14	(3)	222-226	.271
					15	(5)		.0
5	(5)	Me	110-111	.274	16	(4)	187-189	.088
					17	(6)	203-205	.180
6	(6)	Me	96-97	.270	18	(5)	197-198	.051
					19	(7)		.0
7	(7)	H	oil	.293	20	(1)		.0
					21	(6)	283-285	.122

(a); Location of N-chloroacetylaminoethyl substituent on indole ring. (b); Substituent at position 1. (c); Φ for disappearance. (d); Position on the indole ring involved in bond formation in the process of photocyclization. (e); Φ for formation.

Table II. Frontier Electron Densities of Several Species of Indole.

Position	Indole[a]	SOMO of radical cations of		SOMO of
		indole[b]	1-methylindole[b]	indole-1-radical[b]
1	.2066	.0058	.0126	.1062 (.0, .0)[d]
2	.3510	.2004	.2016	.1258 (.062,[e] .025)
3	.3007	.1176	.1334	.2818 (.250, .271)
4	.3300	.0642	.0750 (.088)[c]	.1200 (.150)
5	.0129	.0468	.0330 (.051)	.0004 (.0)
6	.3322	.2196	.2122 (.180)	.1636 (.122)
7	.3031	.0396	.0516 (.108, .0)	.0686

(a); Reactivity index [fr = $(LV)^2 + (HO)^2$][19] calculated by CNDO/2.[20] (b); Calculated by INDO.[22] (c); Values in parentheses are Φ picked out from data in Table I and have a correlation with ED (r = 0.82). (d); In analogy with (c), Φ have a correlation with ED (r = 0.90). (e); Unreliable because of instability of 8.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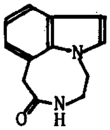
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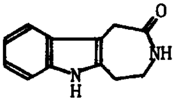
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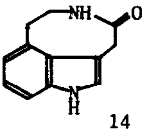
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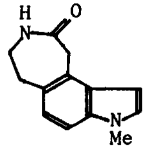
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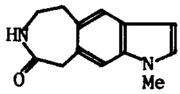
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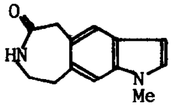
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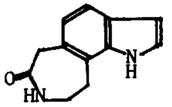
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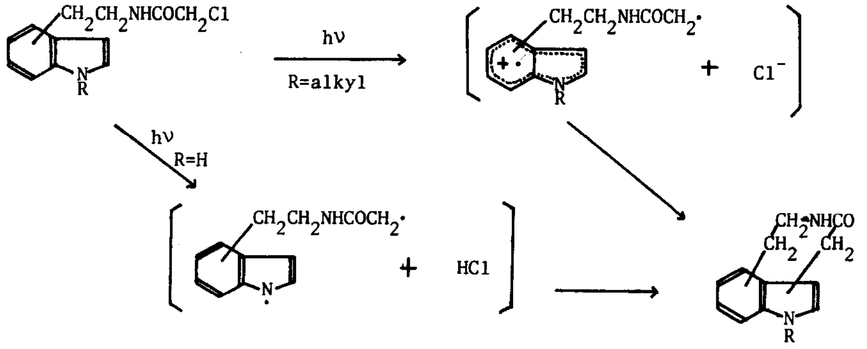
Frontier electron densities of several species of indole in relation to radical reactions have been calculated (Table II) in order to allow comparison with the results in Table I and to narrow down the real reactive species in the photocyclizations. There are no satisfactory correlation (correlation coefficient r = 0.45) between the values in the second column of Table II and the quantum yields for the products (Table I). Accordingly the ground state molecule of indole must not be a reactive species in the photocyclizations.

According to the proposed mechanism, electron densities (ED) of Singly Occupied MO[21] have been calculated next. Because it is difficult to calculate ED of substituted indoles, radical cations of indole and 1-methylindole were chosen. Results calculated by INDO[22] are listed in the third and fourth columns in Table II.[23] Again, there seems to be no simple relation between the quantum yields and ED. However, quantum yields for 1-substituted compounds (9,16,17,18,19) have a correlation (r = 0.82) with the ED of SOMO of the 1-methylindole radical cation. Although quantum yields for 10, 11, 12, 13, 14, 15, 20 and 21 derived from 1-unsubstituted starting materials (2,3,4,7) cannot be explained by the ED of the indole radical cation, they show a good correlation (r = 0.90) with the ED of SOMO of indole-1-radical[24] (the last column in Table II). With allowance for the fact that ring-size effects in the product formation have been neglected in the calculations, the correlations are satisfactory.

In conclusion, the mechanism of the photocyclization of N-chloroacetylaminoethylindoles may be described as shown in the following scheme, and the results presented here may provide the first example for successful application of simple MO calculations to a rather complex molecule, *viz.* the radical reactivity of indole.



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(2) When **i** was irradiated in water, only **ii** was isolated in 18% yield, however, irradiation of **3** now gave two cyclization products **13** (45%) and **12** (7.8%).

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(12) Intermolecular photo-reaction of indole and methyl chloroacetate gave a mixture of seven isomeric methyl indoleacetates.[13] Attempts to separate and analyze quantitatively the products were unsuccessful.

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(14) Quantitative analyses of the products were performed by high-speed liquid chromatography.

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(16) Indole-1-acetamide rearranges photochemically to a mixture containing mainly indole-3-acetamide and indole-6-acetamide,[13] therefore it is necessary to take into account the rearrangement from initially formed **10** and **20** to **11** and **12**. However, since the quantum yield in the disappearance of indole-1-aceatmide is only 0.053, quantum yields in the formation of **10** and **20** must be less than 0.005 in view of the accuracy of the analysis.

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(23) It may be concluded that substituents have a little influence for ED of SOMO, because of little difference between ED of the radical cation of indole and 1-methylindole (r = 0.99).

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