Research on Photochemical and Thermochemical Reactions Between Indole and Quinones in the Absence of Solvent

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The solid state photochemical reaction of indole with 1,4-naphthoquinone yielded 5*H*-dinaphtho[2,3-*a*:2',3'-*c*]carbazole-6,11,12,17-tetrone (**1**) in addition to 2-(3-indolyl)-1,4-naphthoquinone (**2**) which was also the only product in the solution photoreaction. Solventless thermochemical reactions of indole with phenanthrenequinone in the presence or absence of zinc chloride gave 10-(1*H*-indol-3-yl)-9-phenanthrenol (**3**) and 9,10-dihydro-9-(1*H*-indol-3-yl)-10-(3*H*-indol-3-ylidene)-9-phenanthrenol (**4**) or 10,10-di-1*H*-indol-3-yl-9(10*H*)-phenanthrenone (**5**), respectively. All of these products were only obtained in trace amount in corresponding solution reactions, and are different from the adduct 10-hydroxy-10-(1*H*-indol-3-yl)-9(10*H*)-phenanthrenone (**6**) obtained in the solution photoreaction. A possible mechanism for formation of **4** and **5** is described in terms of electron pair donor/acceptor complexation.

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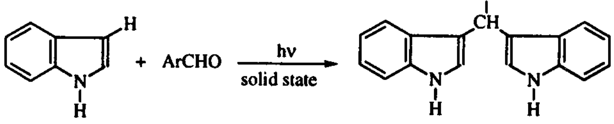
Introduction.

Recently, organic reactions carried out in the absence of solvent have received increasing interest due to their unique selectivities and often high yields [1-2]. This research may contribute to both theoretical and synthetic organic chemistry. Indole and its derivatives such as tryptophan play an important role in many biochemical processes. As a part of the pioneering work on solid-state photoreactions between different molecules, our group has reported the solid state photoreactions of indole with a series of aromatic compounds containing C=X (X = O, N, C) double bonds [3-6].

In general, indole reacts with the carbonyl group in aromatic aldehydes to give a di(3-indolyl)substituted arylmethanes in photoreactions (Scheme 1). We have found that these photoreactions in the solid state provide good yields of products while the corresponding photoreactions carried out in solution gave products in only trace amounts [3].

Scheme 1

Photoreactions Between Indole and Aldehydes



Ar = Ferrocenyl, Nitrophenyl, *etc.*

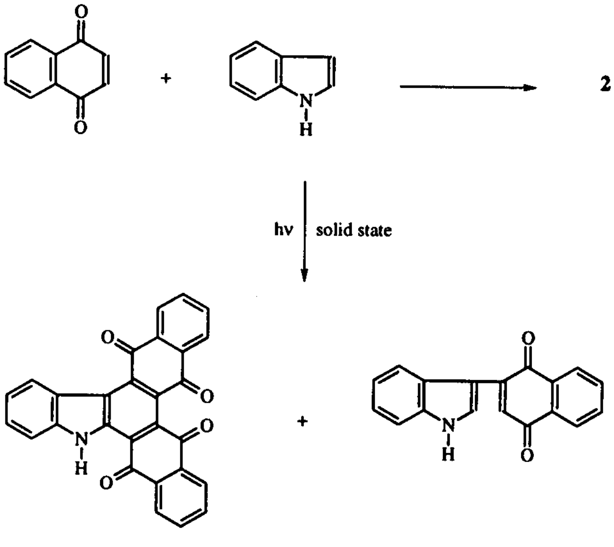
Quinones are also photoreactive species with two carbonyl groups, and many of their derivatives are physiologically active. In this paper, we investigated the photochemical and thermochemical reactions between indole and some important quinones both in solution and in the solid state, and describe a possible mechanism for formation of product **3-5**.

Results and Discussion.

In the solid state, the photoreaction of indole with one equivalent of 1,4-naphthoquinone gave an addition/cyclization product **1** and an addition/oxidation product **2** (^{1}H nmr spectrum of **1** could not be recorded due to its low solubility in common organic solvents). However, a similar photoreaction in solution gave only **2** (Scheme 2). The formation of **1** only in the solid state may be ascribed to the "local concentration effect", *i.e.*, relatively high concentration of reactive species in some parts of the solid state system gives rise to products which otherwise may not be obtained in solution systems.

Scheme 2

Photoreactions Between Indole and 1,4-Naphthoquinone



The photoreaction between indole and *p*-benzoquinone produced a single product both in the solid state and in solution, but it could not be isolated owing to its instability. Irradiation of indole with anthraquinone or 1,4-dihydroxyanthraquinone both in the solid state and in solution did not lead to a detectable reaction product.

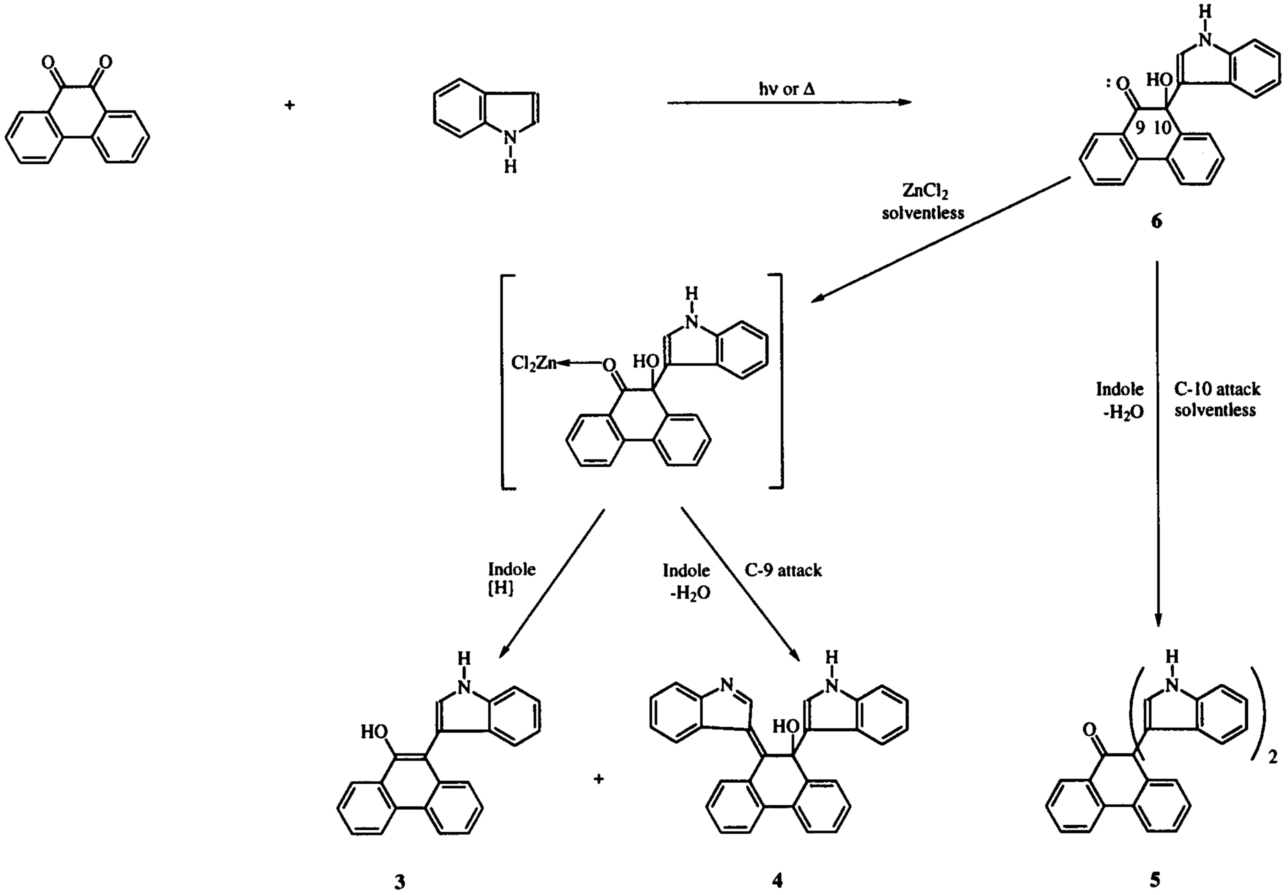
In the absence of solvent, the mixture of phenanthrenequinone with three equivalents of indole was heated to give different products, depending on whether or not zinc chloride was added (Scheme 3). In the presence of zinc chloride, the reaction gave a (3-indolyl)substituted phenanthrenol **3** (an addition/reduction product) and **4** (an addition/condensation product). When no zinc chloride was added, only a di(3-indolyl)substituted phenanthrenone **5** was obtained. It is noteworthy that these reactions could hardly take place in refluxing solvents like benzene (bp 80°), chlorobenzene (bp 132°), or isopropylbenzene (bp 152-154°).

The solution photoreaction of indole with phenanthrenequinone in dichloromethane gave an adduct **6**. In contrast to the photoreactions between indole and an aromatic aldehyde, which only gave a di(3-indolyl)substituted product (Scheme 1), the single 3-indolyl substituted product **6** is stable and obtained in good yield (Experimental 2.3).

Further experiments on reactions between this photoreaction product **6** and indole both in the presence and in the absence of zinc chloride (Experimental 2.4) gave the same corresponding results as those of the reactions between indole and phenanthrenequinone (Experimental 2.2). This indicated that **6** may also be an intermediate in solventless thermochemical reactions of indole with phenanthrenequinone. A possible mechanism for formation of **3**~**5** *via* **6** was assumed to be as shown in Scheme 3. The selectivity of the reactions depends on the relative reactivities of the two possible electrophilic attacking sites of **6**, *i.e.*, C-9 and C-10. In the absence of zinc chloride, the attack by C-10 may be preferable and **5** is the only product. The presence of zinc chloride may increase the electrophilicity of the carbonyl group of **6** through formation of a *n*-electron-pair-donor/v-electron-pair-acceptor complex between the carbonyl group of **6** (C(9)=O) and zinc chloride [7], and therefore the indole molecule is more favorably attacked by C-9 to afford another product **5**. The formation of **3** needs to be clarified in detail; it was assumed that zinc chloride may also favor the reduction of **6** by indole *via* formation of the above *n*-electron-pair-donor/v-electron-pair-acceptor complex.

Scheme 3

Proposed Mechanism for Formation of 3~5 *via* 6 as an Intermediate



EXPERIMENTAL

Melting points were uncorrected. Infrared (ir) spectra were measured on a Nicolet 170SX FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were measured on a JEOL FX-90Q spectrometer with tetramethylsilane as an internal standard. Mass spectra (ms) were determined on a 7070E-HE spectrometer or a HP-5988A mass spectrometer. Ultraviolet (uv) spectra were measured on a Shimadzu UV-240 spectrophotometer, using ethanol as solvent. Elemental analyses were performed on a Yanaco CHN CORDER MT-3 elemental analyzer.

1. Solid State Photochemical Reactions of Indole with Quinones.

1.1. Photoreaction of Indole with 1,4-Naphthoquionone in the Solid State. Formation of 5*H*-Dinaphtho[2,3-*a*:2',3'-*c*]carbazole-6,11,12,17-tetrone (1) and 2-(3-Indolyl)-1,4-naphthoquinone (2).

A mixture of indole (0.23 g, 2 mmoles) and 1,4-naphthoquinone (0.31 g, 2 mmoles) was pulverized in a mortar, followed by irradiation on a pyrex plate using a 400 watt high pressure mercury lamp for 35 hours. After irradiation, the mixture was dissolved in acetone. The insoluble substance was filtered and washed with acetone to give 0.09 g of a red powder, compound **1** (21%); ir (potassium bromide): 3418 (N-H), 1671 (C=O), 1647, 1589 cm^{-1}; ms: m/z 427 (M$^+$), 399, 371, 314, 238, 185, 157.

Anal. Calcd. for $C_{28}H_{13}NO_4$: C, 78.68; H, 3.07; N, 3.28. Found: C, 78.32; H, 3.50; N, 3.26.

The filtrate was concentrated and submitted to silica gel plate chromatography with petroleum ether-dichloromethane as the eluant, giving 0.19 g of a purplish red compound **2** (31%), mp 205-207°; ir (potassium bromide): 3254 (N-H), 1679 (C=O), 1633, 1590 cm^{-1}; ^{1}H nmr (chloroform-d$_1$): δ 7.20-8.20 (m, 10H, ArH), 8.40 (s, 1H, NH); ms: m/z 273 (M$^+$), 271, 245.

Anal. Calcd. for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. Found: C, 78.86; H, 4.28; N, 4.73.

1.2. Photoreaction of Indole with 1,4-Naphthoquionone in Solution.

A mixture of indole (0.117 g, 1 mmole) and 1,4-naphthoquinone (0.150 g, 1 mmole) were dissolved in 50 ml of dichloromethane, followed by irradiation using a 400 watt high pressure mercury lamp under nitrogen for 30 hours. Removal of the solvent followed by chromatography on a silica gel plate using ethyl ether-petroleum ether (v/v 1:1) as the eluant gave 0.09 g of **2** (35%).

1.3. Photoreactions of Indole with *p*-Benzoquinone.

a) Solid-state Reaction.

A mixture of indole (0.117 g, 1 mmole) and *p*-benzoquinone (0.108 g, 1 mmole) were pulverized, followed by irradiation using a 400 watt high pressure mercury lamp for 20 hours. A purple product was detected by thin layer chromatography (tlc), but isolation of the product by silica gel chromatography was not successful.

b) Solution Reaction.

A mixture of indole (0.115 g) and *p*-benzoquinone (0.110 g) was dissolved in 50 ml of dichloromethane. Under nitrogen, the solution was irradiated using a 400 watt high pressure mercury lamp for 30 hours. The tlc test indicated the same product as in a).

1.4. Photoreactions of Indole with Anthraquinone and 1,4-Dihydroxyanthraquinone.

a) Solid-state Reactions.

A mixture of indole and anthraquinone or 1,4-dihydroxyanthraquinone (molar ratio 1:1) was pulverized, followed by irradiation for 100 hours. No reaction was detected by tlc in either mixture.

b) Solution Reactions.

A mixture of indole and anthraquinone or 1,4-dihydroxyanthraquinone (molar ratio 1:1) was dissolved in dichloromethane. The solution was irradiated under nitrogen for 100 hours. No reaction was detected by tlc in either solution.

2. Thermochemical/Photochemical Reactions of Indole with Phenanthrenequinone.

2.1. Thermochemical Reactions of Indole and Phenanthrenequinone in the Absence of Solvent. Formation of 10-(1*H*-Indol-3-yl)-9-phenanthrenol (3), 9,10-Dihydro-9-(1*H*-indol-3-yl)-10-(3*H*-indol-3-ylidene)-9-phenanthrenol (4) and 10,10-Di-1*H*-indol-3-yl-9(10*H*)-phenanthrenone (5).

a) Reaction in the Presence of Zinc Chloride.

Indole (0.51 g, 4.4 mmoles), phenanthrenequinone (0.30 g, 1.4 mmoles), and zinc chloride (0.2 g) were mixed was heated at 160° in an oil-bath with magnetic stirring under nitrogen for 5 hours. After cooling, the reaction mixture was dissolved in 10 ml of dichloromethane. The dark solution was washed with 10 ml of 5% sodium carbonate aqueous solution, and the lower organic layer was separated and dried over anhydrous sodium sulfate. The solution was concentrated and applied to silica gel chromatography (elated with dichloromethane-petroleum ether (v/v 1:1)) to give 0.14 g (31%) of **3** as greenish crystals, mp 141.0-142.5°; ir (potassium bromide): 3411, 1598, 1491, 753 cm^{-1}; ^{1}H nmr (acetone-d$_6$): δ 6.95~7.88 (m, 12H, ArH), 8.55 (m, 1H, ArH), 8.88 (m, 2H, ArH); ms: m/z 309 (M$^+$), 280, 252, 139; uv: λ max (log ε) 220 (4.66), 250 (4.71), 276 (4.36), 304 (4.03) and 361 (3.22) nm.

Anal. Calcd. for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.56; H, 4.79; N, 4.61.

The fraction eluted next gave 0.17 g (28%) of **4** as grey crystals, mp 224.5-226.5°; ir (potassium bromide): 3460, 3402, 1573, 745 cm^{-1}; ^{1}H nmr (acetone-d$_6$): δ 7.02~8.10 (m, 14H, ArH), 8.50 (m, 1H, ArH), 8.88 (m, 2H, ArH); ms: m/z 424 (M$^+$), 407, 307, 280; uv: λ max (log ε): 206 (4.44), 226 (4.44), 250 (4.51), 276 (4.15) and 306 (4.16) nm.

Anal. Calcd. for $C_{30}H_{20}N_2O$: C, 84.88; H, 4.75; N, 6.60. Found: C, 85.04; H, 4.79; N, 6.64.

b) Reaction in the Absence of Zinc Chloride.

Indole (0.51 g, 4.4 mmoles) and phenanthrenequinone (0.30 g, 1.4 mmoles) were mixed and heated under the same condition as in a) for 8 hours. After cooling, 5 ml of dichloromethane was added to the reaction mixture and heated to reflux for 30 minutes, let stand at room temperature for 1 hour, and then filtered. The filtered residue was washed with dichloromethane and recrystallized from acetone-petroleum ether to give 0.14 g of yellow crystalline compound **5**. The filtrate was condensed by removal of solvent and heated under the above condition for 8 hours. The above separation/purification procedure was repeated for this reaction mixture to give 0.08 g of **5**. The total yield was 36%.

Compound **5** had mp 326-328°; ir (potassium bromide): 3410 (N-H), 3337 (N-H), 1672 (C=O), 736 cm^{-1}; ^1H nmr (acetone-d_6): δ 6.62 (t, 1H, ArH), 6.80~7.68 (m, 14H, ArH), 7.82 (m, 1H, ArH), 8.26 (m, 2H, ArH); ms: m/z 424 (M^+), 396, 280, 252; uv: λ max (log ε): 222 (4.88), 240 (4.49), 249 (4.54) and 273 (4.38) nm.

Anal. Calcd. for $C_{30}H_{20}N_2O$: C, 84.88; H, 4.75; N, 6.60. Found: C, 85.09; H, 4.65; N, 6.38.

2.2. Thermochemical Reactions of Indole with Phenanthrenequinone in Solutions.

a) Reaction in the Presence of Zinc Chloride.

Under nitrogen, a solution of indole (0.26 g, 2.2 mmoles) and phenanthrenequinone (0.15 g, 0.7 mmole) in the presence of zinc chloride (0.1 g) in benzene (5 ml) was refluxed for 5 hours. The tlc test indicated trace amount of product **3** and **4** in the reaction mixture. Similar results were given when chlorobenzene and isopropylbenzene were used as solvents in place of benzene.

b) Reaction in the Absence of Zinc Chloride.

Under nitrogen, a solution of 0.26 g of indole and 0.15 g of phenanthrenequinone in 5 ml of benzene was refluxed for 8 hours. The tlc test indicated a trace amount of product **5** in the reaction mixture. Similar results were given when chlorobenzene and isopropylbenzene were used as the solvents in place of benzene.

2.3. Photochemical Reaction of Indole with Phenanthrenequinone in Solution. Formation of 10-Hydroxy-10-(1*H*-indol-3-yl)-9(10*H*)-phenanthrenone (**6**).

Under nitrogen, the solution of indole (0.47 g, 4.0 mmoles) and phenanthrenequinone (0.42 g, 2.0 mmoles) in 20 ml of dichloromethane was irradiated with a 400 watt high pressure mercury lamp for 30 hours. The reaction mixture was concentrated followed by column chromatography, eluted with dichloromethane-petroleum ether (v/v 1:1) to give 0.54 g (61%) of **6** as yellowish crystals, mp 203.5-205.0°; ir (potassium bromide): 3394, 3214, 1688 (C=O), 999 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.24 (br s, 1H, OH), 6.20 (d, 1H, ArH), 6.76~8.04 (m, 12H, ArH), 10.76 (m, 1H, NH); ms: m/z 325 (M^+), 307, 280, 252; uv: λ max (log ε) 217 (4.64), 242 (4.51), 250 (4.50) and 270 (4.16) nm.

Anal. Calcd. for $C_{22}H_{15}NO_2$: C, 81.20; H, 4.65; N, 4.32. Found: C, 81.09; H, 4.72; N, 4.35.

2.4. Thermochemical Reactions between **6** and Indole.

a) Reaction in the Presence of Zinc Chloride.

Under nitrogen, the mixture of 0.26 g (2.2 mmoles) of indole, 0.15 g (0.5 mmole) of **6**, and 0.1 g of zinc chloride was heated at 160° with magnetic stirring for 5 hours. The tlc test showed **3** and **4** as major products.

b) Reaction in the Absence of Zinc Chloride.

Under nitrogen, the mixture of 0.26 g of indole and 0.15 g of **6** was heated at 160° with magnetic stirring for 8 hours. The tlc test indicated that **5** as the major product.

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