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TRIPLET-MEDIATED COUPLING OF 5-BROMO-1,3-DIMETHYLURACIL TO N^b-METHOXYCARBONYLTRYPTAMINE INVOLVING A DOUBLE ELECTRON TRANSFER[1]

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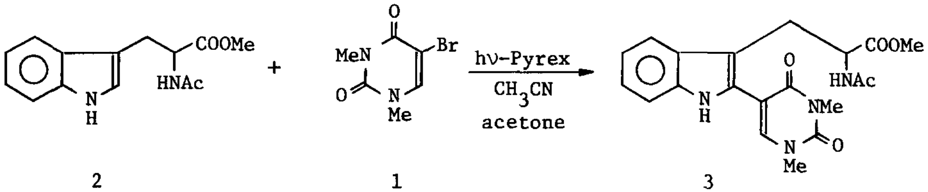
Abstract — On acetone-sensitization, 5-bromo-1,3-dimethyluracil (1) reacts with N^b-methoxycarbonyltryptamine (4) under the assistance of an electron carrier such as 2-methoxynaphthalene to give a coupling product 6. A mechanism involving a double electron transfer via the triplet state of 1 is proposed.

Recently, we reported the acetone-sensitized coupling of 5-bromouracil derivatives to 3-substituted indoles; for example, the coupling of 5-bromo-1,3-dimethyluracil (1) to N^b-acetyltryptophan methyl ester (2) giving regioselectively a coupling product 3 (eq. 1).[2,3] For this reaction, we proposed a mechanism involving an interaction between the triplet state of 1 and 2 followed by an electron transfer process giving radical ions (Scheme 1).[4,5] Among indole derivatives tested, N^b-methoxycarbonyltryptamine (4) gave no coupling product under the same irradiation conditions. However, this difficulty was overcome by adding an electron carrier such as 2-methoxy-, 2,3-dimethoxy- and 1,4-dimethoxynaphthalenes in the reaction system;[4] namely, irradiation of a mixture of 1, 4 and 2-methoxynaphthalene (5) (1 : 2 : 1) in acetonitrile-acetone (3 : 1) with a high-pressure mercury lamp through Pyrex glass gave coupling products 6[3] (38%) and 7[6] (31%) as eq. 2. We now wish to report the details of this reaction supporting a mechanism involving a double electron transfer (Scheme 2). Triplet bromouracil ($^3BrU^*$) interacts with a methoxynaphthalene (NH) to give radical ions, presumably via a triplet exciplex. The naphthalene

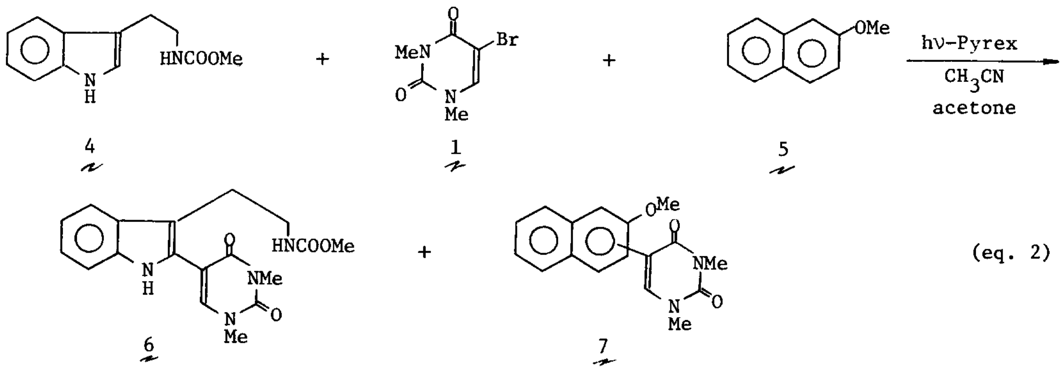


2 1 3

(eq. 1)

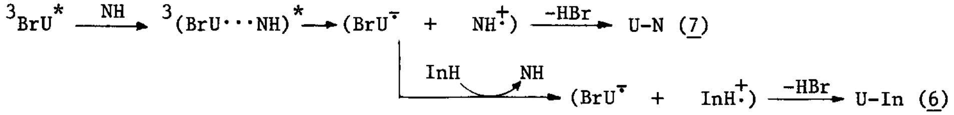
Scheme 1

$$\mathrm{BrU} \xrightarrow{{}^3\text{acetone}^*} {}^3\mathrm{BrU}^* \xrightarrow[(a)]{\mathrm{InH}} \mathrm{BrU}^{\overline{\cdot}} + \mathrm{InH}^{+\cdot} \xrightarrow{-\mathrm{HBr}} \text{In-U}$$



(eq. 2)

Scheme 2



radical cation undergoes either coupling to the bromouracil radical anion yielding 7 or an electron transfer from 4 (InH) followed by coupling between the radical anion and the tryptamine radical cation yielding 6.

Exclusive involvement of the triplet state of 1 in the system is supported by the finding that neither 6 nor 7 was formed by sensitizing the reaction by acetophenone (E_T, 74 kcal/mol), benzophenone (E_T, 69) or triphenylene (E_T, 66.5) in place of acetone.[7] These sensitizers can excite both 4 (E_T, 65) and 5 (E_T, 62) but not 1 (E_T, 74).[9,10] While acetone-sensitized reaction of 1 and 5 in the absence of 4 gave 7 in 65% yield, direct irradiation of 1 and 5 in acetonitrile gave 7 in only 12% yield. The results indicate that the triplet 1 may also be responsible for the formation of 7 in the photoreaction of eq. 2.

The following experimental results are consistent with the occurrence of electron transfer between the radical cations of 5 and 4 as shown in Scheme 2. (1) The competitive coupling of 1 to 4 (E^{ox}, + 0.75 V[12]) and 5 (E^{ox}, + 1.52 V[13]) showed a marked concentration dependency (Figure). (2) Acetone-sensitized photolysis of an acetonitrile solution of a mixture of 1, 2 (E^{ox}, + 0.82 V[12]) and 4 (1 : 2 : 2) gave coupling products 3 (42%) and 6 (22%). This competitive coupling also showed a similar concentration dependency (Figure). These results indicate that the presence of an electron carrier having an oxidation potential (E^{ox}) higher than that of 4 is necessary for the formation of the coupling product 6. (3) The coupling of 1 to 4 in the presence of 5 (eq. 2) was found to be quenched by the addition of catalytic amounts (0.1

equivalent to 1) of quenchers having lower oxidation potentials than that of 4. Thus, the coupling reaction was inhibited by N,N-dimethyl-*p*-anisidine (E^{ox}, + 0.50 V[14]) or N,N,N',N'-tetramethylphenylenediamine (E^{ox}, + 0.36 V[15]) but not by 1,2,4,5-tetramethoxybenzene (E^{ox}, + 0.81 V[16]). Similar quenching effects were also observed in the coupling reaction between 1 and 2 (eq. 1). These results may be explained in terms of a selective electron-transfer quenching of the indole radical cation ($InH^{\cdot+}$ in Scheme 1 and 2) by the aromatics having lower oxidation potentials. (4) When the coupling reaction was carried out using a 1 : 2 : 0.5 molar mixture of 1, 4 and 5 until 60% of 1 was consumed (under these conditions, no naphthalene-uracil coupling product 7 was formed), 80% of 5 remained unreacted in spite of the formation of the coupling product 6 in 38% yield. The large recovery of 5 indicates that it apparently acts as a catalyzer.

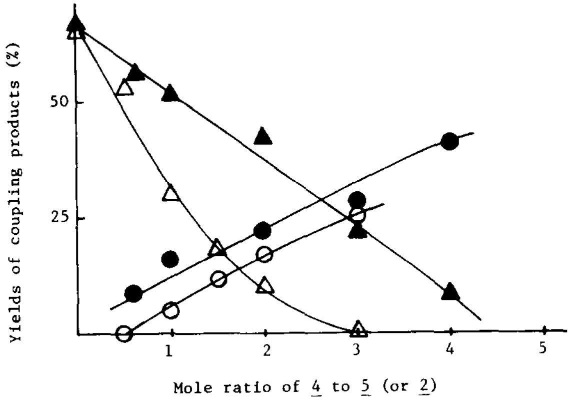


Figure. Dependence of the yields of coupling products on the concentrations of 4. A equimolar mixture of 1 and 5 (or 2) was irradiated in the presence of varying amounts of 4 in CH_3CN-acetone (3 : 1) with light through Pyrex. The plots (○) and (△) show the yields of 6 and 7 in system 4-5, respectively, whereas the plots (●) and (▲) represent the yields of 6 and 3 in system 4-2, respectively.

The available experimental data do not discriminate whether the formation of the second radical-ion pair ($BrU^{\cdot-}$ + $InH^{\cdot+}$) in Scheme 2 occurs from the dissociated naphthalene radical cation or within the intimate radical-ion pair.[17] For this event, one cannot neglect the occurrence of an exciplex substitution reaction[18] in which quenching of the triplet exciplex by an electron donor leads to the formation of another exciplex.[19]

Electron-transfer or redox type photosensitized reactions have drawn much current attention in view of their potential utility in organic synthesis.[20] The present coupling reaction provides the first example of electron-transfer type photosensitization mediated by a triplet state resulting in a coupling reaction, although there have been several precedents for electron transfer from triplet states.[21]

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References and Notes

1. Photoinduced Reactions.111
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4. S. Ito, I. Saito, A. Nakata and T. Matsuura, Nucleic Acids Research Special Publication No. 5, p. 321 (1978).
5. Step (a) may involve intermediate stages such as exciplex and radical-ion pair.
6. Under the conditions, about 80 % of the incident light was absorbed by acetone. Product 7 consisted of an inseparable mixture of two coupling products, mp 56-61 °C; UV (acetonitrile) 216.5 nm (log ε 4.42), 275.5 (3.97), 297sh (3.84), 323sh (3.46); NMR (acetone-d_6) δ 3.32 (s, 3 H), 3.34 (s, 3 H), 3.48 (s, 3 H), 3.50 (s, 3 H), 3.77 (s, 3 H), 4.04 (s, 3 H), 7.80 (s, 1 H), 8.02 (s, 1 H), 6.89-8.30 (m, 12 H). Exact mass, Found: 296.1172. Calcd. for $C_{17}H_{16}O_3N_2$: 296.1160. For other uracil-naphthalene coupling products, the detail will be published in a full paper.
7. These reactions were done with sensitizer concentrations at which 95 % of the incident light was absorbed by the sensitizers. The E_T values of these sensitizers were taken from a literature.[8]
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10. Indoles are known to quench triplet aromatic ketones resulting in decomposition.[11] In accordance with this observation, about 15∿30 % of the tryptamine 4 was recovered after the ketone-sensitized reactions, while 4 was mostly recovered (90 %) after the triphenylene-sensitized reaction.
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17. The coupling reaction of eq. 2 was not appreciably affected by solvent polarity; namely irradiation of a 1 : 2 : 0.5 molar mixture of 1, 4 and 5 in acetonitrile, ethyl acetate and benzene (all containing 25 vol % of acetone) gave 6 in 37, 39 and 34 % yield, respectively.
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19. An attempt to detect some transient species by μ sec flash photolysis was unsuccessful. We are indebted to Dr. S. Kato, Osaka University.
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