THERMODYNAMICALLY CONTROLLED PHOTOCYCLOADDITION OF 5-FLUORO-1,3-DIMETHYLURACIL TO NAPHTHALENES

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Abstract - UV-Irradiation of 5-fluoro-1,3-dimethyluracil (5-FDMU) and 1-acetonaphthone (1a) afforded trans-1,4-adduct, ethenobenzoquinazoline, (2) having an acetyl group at the C-10 bridgehead carbon, together with the cis-isomer (3). The cis-adduct (3) is more fragile than 2 in the dark at ambient temperature, and is more quickly converted back to the starting 1a and 5-FDMU through cycloreversion. Thus, the trans-adduct (2) comes to the predominant product when irradiation is prolonged. Similar irradiation of 1-naphthonitrile afforded cis-ethenobenzoquinazoline-10-carbonitrile (6) and the trans-isomer (7) as the kinetically controlled cycloadducts together with cis-ethenobenzoquinazoline with a CN group on the benzene moiety (5) as thermodynamically controlled product.

Photocycloaddition reactions involving aromatic and heteroaromatic compounds have been recognized to give rise to the formation of a variety of complicated unique ring systems in one step, and hence these reactions have been studied extensively from both the synthetic and mechanistic point of view. In the course of our continuing studies on the photochemical modification of the pyrimidine ring, we have recently reported that UV-irradiation of a solution of 5-fluoro-1,3-dimethyluracil (5-FDMU) and naphthalene in protic media effected a substitution reaction to afford 5-(1-naphthyl)uracil as the major product. By contrast, when the solution was irradiated in aprotic media, 1,4-cycloaddition proceeded stereoselectively to give a cis-ethenobenzoquinazoline derivative in high yield. In an attempt to develop new aspects of this photocycloaddition, we have intended to apply the present photoreaction to reaction with naphthalenes having an electron-withdrawing group at C-1. In the
present paper, we wish to report our findings that the photoreaction of 5-FDMU and 1-acetonaphthone (1a) provides the thermodynamically controlled adduct, trans-ethenobenzoquinazoline-2,4-dione (2).

A solution of 5-FDMU and 1-acetonaphthone (1a) in cyclohexane, when irradiated externally with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ>300 nm) for 4 h, gave a trans-barrelene (10-acetyl-trans-ethenobenzoquinazoline, 2) in 42% yield, wherein the ethylene bridge stands trans to the corresponding 10a-H and 4a-F, as the major product and cis-isomer (3) in 22% yield as a minor product, together with a trace amount of a novel cycloadduct, 9-acetyl-1,3-dimethyl-5,6,11-methenobenzo[4,5]cyclohepta[2,1-d]pyrimidine-2,4-dione (4) (Scheme 1).

The stereochemistry of 2 was determined with the aid of NOE experiments. Irradiation of the H-10a proton significantly affected the H-9 aromatic proton (1.4%), as well as H-10 and N1-CH₃ (8.4%), indicating that the stereochemistry of 2 is trans, while stereoisomer (3) showed significant enhancement of signals at vinylic proton H-11 (1.0%), N1-CH₃ (7.6%), and C10-COCH₃ (2.8%) on irradiation of the H-10a proton, thus supporting the stereochemistry of 3 to be cis.

It is important to note that both of the adducts (2 and 3) bearing an acetyl group at the bridge-head, are fragile in the dark at ambient temperature, and are converted back to the starting 1a and 5-FDMU through cycloreversion (Scheme 2). In addition, the half-life of 2 at 20°C is longer (14 h) than that of 3.

![Scheme 1](image-url)
(8 h). This disparity between their thermolabilities should be responsible for the formation of the novel trans-isomer (2)\textsuperscript{5} through a photochromic process. That is, the initially produced cis-isomer (3) as the kinetically controlled product, undergoes cycloreversion to the starting materials during irradiation, which are again subjected to cycloaddition, leading to the accumulation of the more stable component (2) in the reaction mixture. Short period-irradiation (1 h) of the reaction mixture produced approximately equal amounts of 2 and 3 with large amounts of unchanged 5-FDMU and 1a (>90%), while prolonged irradiation (10 h) exclusively furnished the thermodynamically controlled trans-isomer (2) (Scheme 1), rationalizing the above explanation.

[Chemical structures and reactions depicted]

MO calculations\textsuperscript{6} showed that the heat of formation of the trans-isomer (-61.5 kcal) is lower than that of the cis-isomer (-31.5 kcal) by 30 kcal, suggesting that the cis-isomer is the kinetically controlled product, while the trans-isomer can be regarded as a thermodynamically controlled product. Similar irradiation of a mixture of 5-FDMU and 1-naphthonitrile (1b) in cyclohexane for 3 h furnished cis-ethenobenzoquinazoline-9-carbonitrile (5) (69% yield), cis-ethenobenzoquinazoline-10-carbonitrile (6) (28% yield), and the trans isomer (7) albeit in low yield (2% yield) (Scheme 3). The adduct (5) is stable at room temperature, while the adducts having a CN group at the bridgehead are thermochemically unstable (Scheme 2). As expected, the half-life of 6 is appreciably shorter than that of...
the trans isomer (7).

Prolonged irradiation (10 h), however, resulted in the formation of 5 as the major product (45 %), and the formation of 6 and 7 was not detected (Scheme 3). Presumably, the present reaction proceeded with less regioselectivity than with 1a, resulting in the formation of thermally stable isomer (5), together with variable amounts of 6 and 7. During prolonged irradiation times, 6 and 7 would presumably be converted into the stable 5 through cycloreversion.

Thus, the present study provides the first synthesis of a trans-ethenobenzof[\(f\)]quinazoline derivative by introducing an acetyl group onto the naphthalene ring at the C-1 position.

**EXPERIMENTAL**

NMR spectra were measured with a JEOL JNM-EX400 (400 MHz) spectrometer, and \(^1\)H-NMR chemical shifts are given on the \(\delta\) (ppm) scale based on those of the signals of solvents; CDCl\(_3\) (\(\delta\) 7.26), C\(_6\)D\(_6\) (\(\delta\) 7.15). MS spectra and high-resolution MS (HRMS) spectra were recorded with LEOL JMS-HX110 (FAB). HPLC was conducted on a Shim-pac PREP-Sil (H) (25 cm x 20 mm i. d.) (silica gel), using a LC-6A apparatus (Shimadzu, Kyoto) with monitoring at 254 nm. UV-Irradiation was carried out externally with a 500 W high-pressure mercury
Photoreaction of 5-FDMU with naphthalenes (1a, 1b)---- An equivalent molar solution (1.5 mM) of 5-FDMU and a naphthalene in cyclohexane (160 mL) was put portion-wise (5 mL each) into 32 degassed Pyrex tubes, and irradiated externally at rt. The reaction mixture was concentrated in vacuo, and the residual oil was submitted to HPLC with 25% ethyl acetate in hexane.

10-Acetyl-4a-fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-trans-5,10-ethenobenzof[4]quinazoline-2,4-dione (2): Colorless crystals; mp, not determined (decomposed at 20°C with a half-life of 14 h). 1H-NMR (CDCl3) δ 2.53 (3H, s, C10-COCH3), 2.93 (3H, s, N1-CH3), 3.11 (3H, d, J=0.5 Hz, N3-CH3), 3.86 (1H, d, J=28.9 Hz, H-10a), 4.57 (1H, br t, J=5.5, 6.4 Hz, H-5), 6.51 (1H, dd, J=7.9, 6.4 Hz, H-12), 6.90 (1H, d, J=7.9 Hz, H-11), 6.98 (1H, d, J=7.5 Hz, H-9), 7.15–7.25 (2H, m, H-7–H-8), 7.37 (1H, d, J=7.7 Hz, H-6). NOE: H-10a with N1-CH3 (8.4%), H-9 (1.4%). FABMS m/z (%): 329 (M+H)+, 309, 159. HRFABMS: Calcd for C18H18N2O3F: 329.1301. Found: 329.1311.

10-Acetyl-4a-fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-cis-5,10-ethenobenzof[4]quinazoline-2,4-dione (3): Colorless crystals; mp, not determined (decomposed at 20°C with a half-life of 8 h). 1H-NMR (CDCl3) δ 2.60 (3H, s, N4-CH3), 2.61 (3H, s, C10-COCH3), 3.01 (3H, s, N1-CH3), 4.02 (1H, d, J=29.2 Hz, H-10a), 4.55 (1H, t, J=1.6 Hz, H-5), 6.62 (1H, dd, J=1.6, 8.0 Hz, H-11), 6.86 (1H, dd, J=6.0, 8.0 Hz, H-12), 7.18 (1H, d, J=7.0 Hz, H-6), 7.20–7.28 (2H, m, H-7–H-8), 7.86 (1H, d, J=7.0 Hz, H-9). NOE: H-5 with H-6 (7.3%), H-12 (7.5%); H-10a with N1-CH3 (7.6%), C10-COCH3 (2.8%), H-11 (1.0%); C10-COCH3 with H-10a (7.4%), N1-CH3 (2.3%); H-12 with H-5 (10%), H-11 (6.3%); H-11 with C10-COCH3 (9.6%), H-12 (13.1%).

9-Acetyl-4a-fluoro-4a,10,11,11a-tetrahydro-5,10,11-metheno-1,3-dimethylbenzo[4,5]cyclohepta[1,2-d]pyrimidine-2,4-dione (4): Colorless prisms; mp 190-192°C. 1H-NMR (CDCl3) δ 2.61 (3H, s, C9-COCH3), 2.61 (1H, ddd, J=8.1, 6.0, 6.0 Hz, H-11), 2.75 (3H, s, N1-CH3), 2.95 (3H, s, N1-CH3), 3.40 (1H, ddd, J=6.6, 6.0, 5.1 Hz, H-12), 3.51 (1H, d, J=8.1, 6.0 Hz, H-10), 4.11 (1H, ddd, J=11.8, 5.1, 2.9 Hz, H-5), 4.29 (1H, ddd, J=27.0, 6.0, 2.9 Hz, H-11a), 6.99 (1H, d, J=7.7 Hz, H-6), 7.14 (1H, t, J=7.7 Hz, H-8), 7.68 (1H, d, J=7.7 Hz, H-8). NOE: H-5 with H-6 (2.4%), H-12 (2.9%); H-6 with H-5 (1.5%); H-7 (9.0%); H-8 with H-7 (4.4%), C10-COCH3 (6.8%); H-10 with H-11 (7.6%) (9.6%), H-12 (3.3%); H-11 with H-10 (7.3%), H-11a (7.7%), H-12 (3.4%), N1-CH3 (2.1%); H-12 with H-5 (4.3%), H-10 (2.7%), H-11 (2.3%). FABMS m/z (%): 329 (M+H)+. HRFABMS: Calcd for C18H18N2O3F: 329.1301. Found: 329.1309.

4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-2,4-dioxo-cis-5,10-ethenobenzof[4]quinazoline-9-carbonitrile (5): Colorless prisms; mp 156-158°C. 1H-NMR (C6D6) δ 2.26 (3H, d, J=0.7 Hz, N3-CH3), 2.75 (3H, s, N1-CH3), 3.01 (1H, d, J=31.5, 2.6 Hz, H-10a), 4.28 (1H, ddd, J=6.4, 2.6, 1.2 Hz, H-10), 4.49 (1H, ddd, J=6.6, 6.0, 1.3 Hz, H-5), 5.95 (1H, ddd, J=7.4, 6.6, 1.2 Hz, H-11), 6.12 (1H, ddd, J=7.4, 6.4, 1.3 Hz, H-12), 6.32 (1H, t like, J=7.5, 7.8 Hz, H-7), 6.59 (1H, dd, J=7.8, 1.1 Hz, H-8), 6.67 (1H, dd, J=7.5, 1.1 Hz, H-6). NOE: H-10a with H-10
(7.0%), N1-CH3 (5.2%), H-11 (1.7%), H-12; H-11 with H-12 (6.1%), H-10 (7.3%), H-10a (1.9%). FABMS m/z (%): 312 (M + H)+, 159. HRFABMS: Calcd for C17H15N2O3F: 312.1148. Found: 312.1119.

4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethy-2,4-dioxo-cis-5,10-ethenobenzo[f]quinazoline-10-carbonylitrile (6): Colorless crystals; mp, not determined (decomposed at 20°C with a half-life of 6 h). 1H-NMR (CDCl3) δ: 2.66 (3H, s, N1-CH3), 3.41 (3H, s, N3-CH3), 4.01 (1H, d, J = 28.8 Hz, H-10a), 4.69 (1H, dt, J = 1.6, 6.0 Hz, H-5), 6.78 (1H, dd, J = 1.6, 7.6 Hz, H-11), 6.82 (1H, dd, J = 6.0, 7.6 Hz, H-12), 7.24 (1H, dd, J = 1.0, 7.5 Hz, H-6), 7.30 (1H, dt, J = 1.0, 7.5 Hz, H-8), 7.35 (1H, dt, J = 1.0, 7.5 Hz, H-7), 7.66 (1H, d, J = 7.5 Hz, H-9). NOE: H-10a with N1-CH3 (9.1%), H-11 (5.5%), H-12 (1.0%); H-5 with H-6 (10.4%), H-12 (12.2%).

4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethy-2,4-dioxo-trans-5,10-ethenobenzo[f]quinazoline-10-carbonylitrile (7): Colorless crystals; mp, not determined (decomposed at 20°C with a half-life of 24 h). 1H-NMR (CDCl3) δ: 3.20 (3H, s, N3-CH3), 3.45 (3H, s, N1-CH3), 3.67 (1H, d, J = 28.4 Hz, H-10a), 4.76 (1H, t, J = 6.8 Hz, H-5), 6.56 (1H, dd, J = 6.8, 7.2 Hz, H-12), 6.65 (1H, d, J = 7.2 Hz, H-11), 7.35-7.45 (2H, m, H-7, H-8), 7.48 (1H, dd, J = 12, 7.2 Hz, H-6), 7.7 (1H, d, J = 7.4 Hz, H-9). NOE: H-5 with H-12 (10.6%), H-6 (9.1%); H-10a with N1-CH3 (8.9%); H-11 with H-12 (5.6%); N1-CH3 with H-10a (6.1%). FABMS m/z (%): 312 (M + H)+. HRFABMS: Calcd for C17H15N2O3F: 312.1148. Found: 312.1159.

REFERENCES AND NOTES


5. Previously we have reported that photoreaction with 5-FDMU and naphthalene and its 2-substituted derivatives stereospecifically gave cis-ethenobenzoquinazolines in fair yields.

6. MO calculation was performed by the AM1 method with MOPAC on CAChe Work-system (Release 3.7; Cache Scientific, Inc.).