Intramolecular Photocyclization in Quinone-Bearing Oligopeptides

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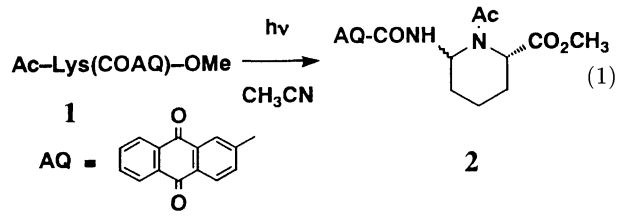
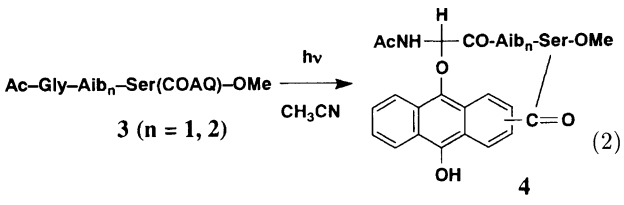
Synopsis. The photoexcited anthraquinone moiety (AQ) of (*N*-acetylglycyl)oligopeptide-linked anthraquinones in acetonitrile abstracted intramolecularly the hydrogen in the α-methylene of glycine to give a sole isomeric ring-closure product. Site-selectivity was produced mainly by a difference in the spatial distance between the C=O of AQ and reactive CH_2.

The interaction of pigments with proteins is a current topic for physical, organic, and biological chemistry.[1] For a model we have already reported on the photoreaction of synthetic quinone-bearing oligopeptides as well as the interaction of the quinone with the oligopeptide.[2—4] Irradiation of terminal-protected lysine **1** with an anthraquinone moiety (AQ)[5] at the side chain through an amido bond induced *intermolecular* hydrogen abstraction by a photoexcited AQ from the ε-methylene site (AQCONHC$\underline{H}_2$–) in the other molecule, to give cyclic compounds **2**, as shown in Eq. 1.[2]



(1)

The photoreaction of acetylglycine-linked serine **3** with an AQ through an ester bond afforded another cyclic compound **4** through *intramolecular* hydrogen abstraction from α-CH_2 of the glycine (Eq. 2).[3]



(2)

In this paper we report on the photoreaction of anthraquinone-bearing oligopeptides **5** with a glycine through an amide bond, possessing two reactive methylene sites as a hydrogen donor, the α-methylene group of Gly and the ε-methylene group of Lys-residue.

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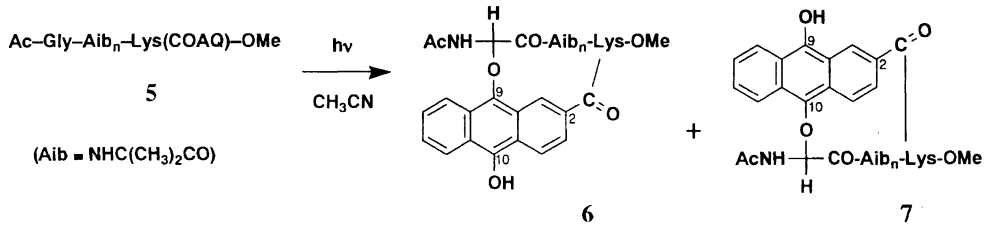
Results and Discussion

Thirty-minute irradiation of an argon-saturated acetonitrile solution of Ac–Gly–Lys(COAQ)–OMe **5a** (1×10^{-3} mol dm^{-3}) with a high-pressure mercury arc lamp through an aqueous $CuSO_4$ solution filter (selective irradiation of the AQ) at room temperature gave cyclized **6a** (8%) with the ether linkage (C9–O–$^{\alpha}$C) being the sole isolable product after column chromatography over silica gel (see Table 1). The structure of photoproduct **6a** was confirmed based on its spectral data (^{1}H NMR, IR, MS, UV, and fluorescence, see Experimental section). Upon similar irradiation, **5b** with one Aib residue predominantly afforded **7b** (40%) with different bonding (C10–O–$^{\alpha}$C) from that of **6a**. In the photoreaction of **5c** with an Aib–Aib spacer, trace amounts of **6c** and **7c** could be detected in the reaction mixture by means of ^{1}H NMR. Table 1 gives that the yields of **6** and **7**, the conversion of **5**, and the quantum yield of the disappearance of **5** depended upon the number (n) of Aib residues as well as in the photoreaction of **3** to **4**.[3] The length of oligopeptide link (–Aib$_n$–) greatly affected the photoreactivity and site-selectivity. The above-mentioned photoreactions should be initiated by an intramolecular hydrogen abstraction of AQ from glycyl methylene and should proceed through a recombination of the produced biradical (see Ref. 3). It should be noted that the photoreaction of **5** gave no piperidine derivatives, as shown in Eq. 1, which were given in the photoreaction of lysine–anthraquinone molecules **1** with no glycine residue in the molecule; the formation of piperidines should occur through intermolecular hydrogen abstraction of photoexcited AQ from lysyl ε-methylene and a successive intramolecular attack of the radical produced on the ε-position to the lysyl α-amido C=O followed by a special rearrangement (see Ref. 2). These results indicate that the methylene site of Gly is more reactive than that of AQCONHC$\underline{H}_2$–, and that intramolecular hydrogen abstraction is more favored than the intermolecular type under the above-mentioned photoreaction conditions.

In conclusion, the photoreaction of **5** did not take the path of Eq. 1, but that of Eq. 2, i.e., the photoexcited AQ of **5** in acetonitrile could not *intermolecularly* abstract the hydrogen atom in the ε-methylene group of Lys (AQCONHC$\underline{H}_2$–), but did *intramolecularly* abstract the hydrogen in the α-methylene of Gly to give exclusively a sole ring-closure product (**6** or **7**) with an isomeric ether linkage (C9–O–$^{\alpha}$C or C10–O–$^{\alpha}$C).

Table 1. Photochemical Reaction of Acetylglycine–Anthraquinone Molecules



	n	Yield/%[a] 6	Yield/%[a] 7	Conversion of 5/%	Φ[b]
5a	0	8	0	48	0.20
5b	1	Trace	40	70	0.37
5c	2	Trace	Trace	31	0.22

a) Isolated yield based on consumed **5**. b) Quantum yield of disappearance of **5**, upon irradiation of 313-nm light.

The pathway of the photoreaction including the site-selectivity should be determined by the inter- and intramolecular spatial average distance between the C=O of AQ and the reactive CH_2 groups under the reaction conditions.

Experimental

General. All of the equipment has already been reported, as well as the procedures for the photoreaction.[3] According to similar methods reported previously,[3] the hydrogenation of Boc–Lys(Z)–OMe and successive amidation by AQCOCl gave Boc–Lys(COAQ)–OMe (50%, mp 168—170 °C), which was deprotected, coupled with Boc–Gly–Aib$_n$–OH, deprotected and acetylated to afford Ac–Gly–Aib$_n$–Lys(COAQ)–OMe (**5**) as pale-yellow solids. The full synthetic procedures were discussed in the master's thesis of Hashimoto.[6]

Ac–Gly–Lys(COAQ)–OMe (5a): 50% (2-step yield from Boc–Lys(COAQ)–OMe), mp 179—181 °C; UV (CH_3CN) 256 and 326 nm; IR (KBr) 3296 (NH), 1753, 1676, and 1642 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.50 (2H, m), 1.73 (3H, m), 1.95 (1H, m), 2.02 (3H, s), 3.49 (1H, dd, J=6 and 13 Hz), 3.55 (1H, dd, J=6 and 13 Hz), 3.76 (3H, s), 3.94 (1H, dd, J=5 and 16 Hz), 4.02 (1H, dd, J=5 and 16 Hz), 4.64 (1H, dt, J=4 and 8 Hz), 6.59 (1H, br), 6.81 (1H, d, J=8 Hz), 7.21 (1H, t, J=5 Hz), 7.84 (2H, m), 8.32 (2H, m), 8.36 (1H, dd, J=1.5 and 8 Hz), 8.39 (1H, d, J=8 Hz), and 8.69 (1H, d, J=1.5 Hz); MS m/z 494 (MH$^+$). Found: C, 63.11; H, 5.55; N, 8.52%. Calcd for $C_{26}H_{27}N_3O_7$: C, 63.27; H, 5.51; N, 8.52%.

Ac–Gly–Aib–Lys(COAQ)–OMe (5b): 55%, mp 185—187 °C; UV (CH_3CN) 256 and 327 nm; IR (KBr) 3303 (NH), 1741, 1676, and 1658 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.50 (3H, s), 1.54 (3H, s), 1.65—1.77 (5H, m), 1.95 (1H, m), 2.05 (3H, s), 3.46 (1H, dd, J=5 and 14 Hz), 3.54 (1H, dd, J=5 and 14 Hz), 3.74 (3H, s), 3.85 (2H, d, J=6 Hz), 4.60 (1H, dt, J=4 and 8 Hz), 6.94 (1H, br), 7.01 (1H, s), 7.06 (1H, d, J=8 Hz), 7.84 (2H, m), 7.97 (1H, t, J=5 Hz), 8.30 (1H, m), 8.34 (1H, m), 8.37 (1H, d, J=8 Hz), 8.40 (1H, dd, J=2 and 8 Hz), and 8.70 (1H, d, J=1 Hz); MS m/z 579 (MH$^+$). Found: C, 61.99; H, 5.95; N, 9.57%. Calcd for $C_{30}H_{34}N_4O_8$: C, 62.27; H, 5.92; N, 9.69%.

Ac–Gly–Aib$_2$–Lys(COAQ)–OMe (5c): 61%, mp 170—172 °C; UV (CH_3CN) 256 and 326 nm; IR (KBr) 3303 (NH), 1736, 1674, 1653, and 1639 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.37 (3H, s), 1.41 (3H, s), 1.44 (3H, s), 1.50 (3H, m), 1.54 (3H, s), 1.78 (2H, m), 1.91 (1H, m), 2.08 (3H, s), 3.37 (1H, m), 3.63 (1H, m), 3.71 (3H, s), 3.72 (1H, dd, J=6 and 16 Hz), 3.88 (1H, dd, J=6 and 16 Hz), 4.62 (1H, dt, J=3.5 and 9.5 Hz), 6.71 (1H, s), 6.81 (1H, s), 7.03 (1H, br), 7.33 (1H, d, J=9 Hz), 7.81 (2H, m), 7.97 (1H, t, J=5.5 Hz), 8.31 (2H, m), 8.33 (1H, d, J=8 Hz), 8.36 (1H, dd, J=2 and 8 Hz), and 8.74 (1H, d, J=1.5 Hz); MS m/z 664 (MH$^+$). Found: C, 61.41; H, 6.48; N, 10.41%. Calcd for $C_{34}H_{41}N_5O_9$: C, 61.52; H, 6.23; N, 10.55%.

6a: Pale yellow solids; mp 151—153 °C; UV (CH_3CN) 257 and 280 (sh) nm; fluorescence (2-MeTHF, 77 K, excitation at 275 nm) 418, 448, 483, and 524 nm; IR (KBr) 3450 (OH, NH), 1723, and 1668 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.50 (3H, s), 1.57 (4H, m), 1.81 (2H, m), 3.34 (1H, m), 3.61 (1H, m), 3.82 (3H, s), 4.64 (1H, q, J=7 Hz), 5.03 (1H, d, J=9 Hz), 5.32 (1H, d, J=8.5 Hz), 6.04 (1H, br), 7.36 (1H, d, J=1 Hz), 7.52 (2H, m), 7.73 (1H, t, J=1 Hz), 7.90 (1H, d, J=1 Hz), and 8.12 (3H, m); MS m/z 494 (MH$^+$). Found: m/z 494.1933. Calcd for $C_{26}H_{28}N_3O_7$: MH, 494.1927.

7b: Pale yellow solids; mp 213—216 °C; UV (CH_3CN) 280 nm; fluorescence (2-MeTHF, 77 K, excitation at 275 nm) 417, 446, 480, and 519 nm; IR (KBr) 3350 (OH, NH), 1738, and 1657 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.44 (2H, m), 1.60 (3H, s), 1.61 (3H, s), 1.76 (3H, m), 1.86 (1H, m), 2.17 (3H, s), 3.37 (1H, m), 3.52 (1H, m), 3.83 (3H, s), 4.49 (1H, m), 4.82 (1H, d, J=9 Hz), 5.40 (1H, d, J=9 Hz), 5.82 (1H, s), 6.36 (1H, d, J=8 Hz), 7.07 (1H, br), 7.22 (1H, s), 7.50 (1H, dt J=1 and 7 Hz), 7.70 (1H, dd, J=1 and 7 Hz), 7.73 (1H, dt J=1.5 and 9 Hz), 7.95 (1H, d, J=8 Hz), 8.11 (1H, dd, J=1 and 8 Hz), 8.16 (1H, d, J=8 Hz), and 8.24 (1H, d, J=1.5 Hz); MS m/z 579 (MH$^+$). Found: m/z 579.2468. Calcd for $C_{30}H_{35}N_4O_8$: MH, 579.2455.

References

1) Reviews for interaction of quinones with proteins, see: "The Chemistry of the Quinonoid Compounds," ed by S. Patai, John Wiley & Sons, London (1974); R. H. Thomson,

"Naturally Occurring Quinones III," Chapman and Hall, New York (1987); "The Chemistry of the Quinonoid Compounds," ed by S. Patai and Z. Rappoport, John Wiley & Sons, Chichester (1988), Vol. 2.

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3) K. Maruyama, M. Hashimoto, and H. Tamiaki, *J. Org. Chem.*, **57**, 6143 (1992).

4) H. Tamiaki and K. Maruyama, *Chem. Lett.*, **1993**, 1499.

5) The following abbreviations are used in this paper; Gly=glycine ($NHCH_2CO$), Aib=α-methylalanine ($NHC(CH_3)_2CO$), Ser = L-serine ($NHCH(CH_2OH)CO$), Lys = L-lysine ($NHCH(CH_2CH_2CH_2CH_2NH_2)CO$), Boc = *t*-butoxycarbonyl, Z = benzyloxycarbonyl, and AQ = 2-anthraquinonyl.

6) M. Hashimoto, Master Thesis, Kyoto University, Kyoto, 1990.