Synthesis and Catalytic Properties of 5-Deazaflavo-6,9-quinones

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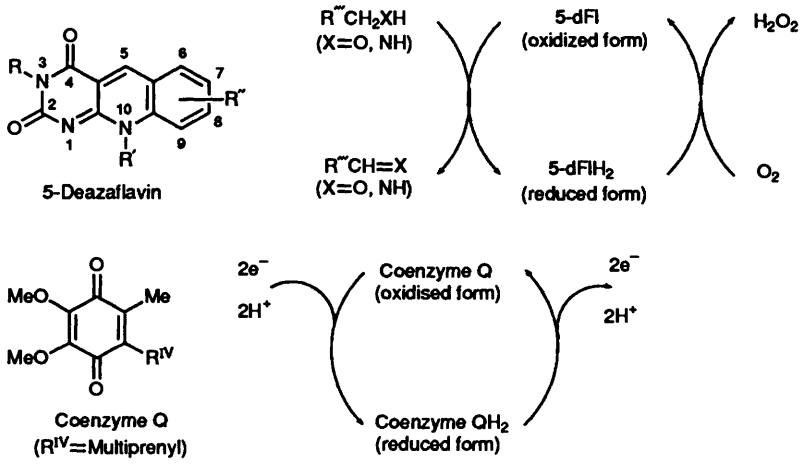
Novel 5-deazaflavo-6,9-quinones, which can be regarded as chemical hybrids of 5-deazaflavin and coenzyme Q, were designed and synthesized in a search for more powerful autorecycling redox catalysts for amine oxidation. 9-Methoxy-5-deazaflavins, which were synthesized from 6-aminouracils and 2,3-dimethoxybenzaldehydes, were exposed to oxidation with cerium ammonium nitrate in aqueous acetonitrile to give 5-deazaflavo-6,9-quinones. While 8-unsubstituted 5-deazaflavo-6,9-quinones thus obtained were unstable in the amine oxidation, 8-methoxy-5-deazaflavo-6,9-quinones were rather stable under the same conditions and showed an autorecycling amine-oxidizing ability.

5-Deazaflavin, in which N-5 of flavin is replaced by CH, has been extensively studied as a model system in investigations of the mechanism of flavin-catalysed reactions.[1–3] Syntheses of 5-deazaflavins and their biomimetic reactions have been accomplished.[4–6] For example, 5-deazaflavins showed strong autorecycling redox power in model alcohol and amine dehydrogenase oxidations.[7,8]

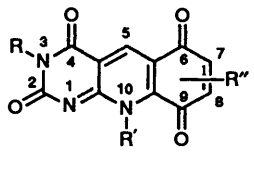
In the course of the oxidation by 5-deazaflavin, the 5-deazaflavin plays a role as an autorecycling catalyst; the substrate is oxidized and 5-deazaflavin (5-dFl) is reduced to the 1,5-dihydro-5-deazaflavin (5-dFlH_2), which is easily reoxidized by air to the original 5-dFl and it takes part in another cycle of amine oxidation (Scheme 1).



Scheme 1

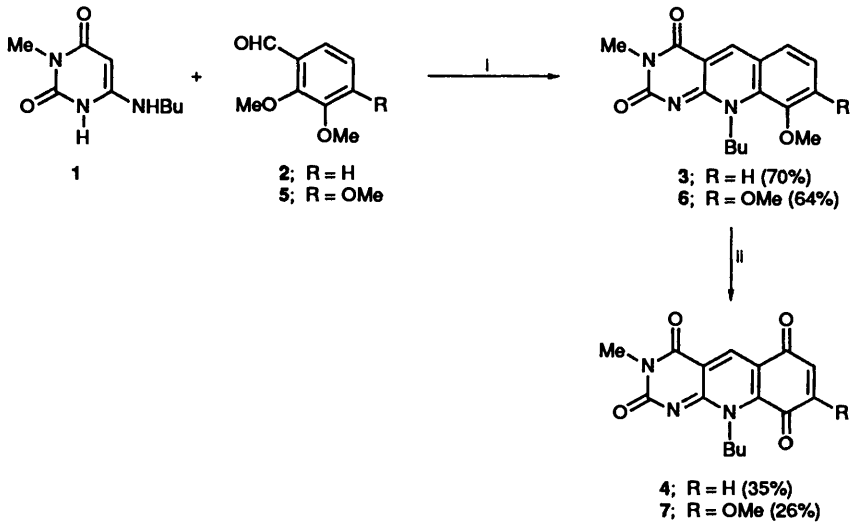
In the meantime, coenzyme ubiquinone (Coenzyme Q), which is a 1,4-benzoquinone derivative, is playing an important role as an electron carrier in the electron-transport system of the respiratory chain.

In order to develop a newer and more powerful autorecycling catalyst than 5-deazaflavin, we planned to synthesize a novel type of 5-deazaflavo-6,9-quinone which is considered to be a chemical hybrid of 5-deazaflavin and coenzyme Q.



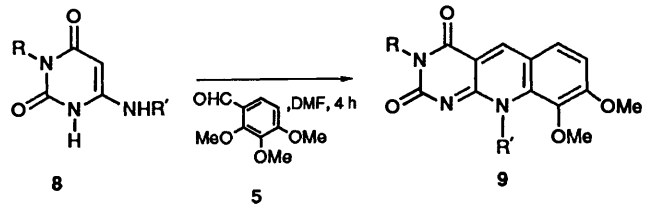
Condensation of 6-butylamino-3-methyluracil **1** and 2,3-dimethoxybenzaldehyde **2** in dimethylformamide (DMF) gave 10-butyl-9-methoxy-3-methyl-5-deazaflavin **3** in moderate yield (Scheme 2). In most cases, conversion of the 9-methoxy-5-deazaflavin **3** into the corresponding 5-deazaflavo-6,9-quinone **4** by oxidation proved difficult, because undesired oxidized products were obtained, but succeeded only when cerium(IV) ammonium nitrate (CAN) was used as the oxidizing agent, even though it gave a low yield. Proton NMR spectra of 5-deazaflavo-6,9-quinones **4** showed a reasonable change in both chemical shift and coupling pattern of the C-7 and -8 protons of the 5-deazaflavin skeleton compared with those of 5-deazaflavin itself.

First, the oxidation of benzylamine with 10-butyl-3-methyl-5-deazaflavo-6,9-quinone **4** was tried under the conditions described in the Experimental section. However, it is difficult to discuss the oxidizing power of the flavoquinones **4** because they degrade under the conditions used. The occurrence of the degradation seemed to be because of nucleophilic attack of the amino function at C-8 of quinones **4**, which occurred predominantly. In order to prepare a more stable compound, another 5-deazaflavoquinone derivative having a substituent at C-8 was synthesized starting from the uracil **1** and 2,3,4-trimethoxybenzaldehyde **5**. 10-Butyl-8,9-dimethoxy-3-methyl-5-deazaflavin **6** thus obtained was also converted into the corresponding 5-deazaflavo-6,9-quinone, compound **7**, by CAN. The oxidation of benzylamine with compound **7** was attempted under the same conditions and it was found that the reaction was facilitated without decomposition to give benzaldehyde in 120% yield based on quinone **7**. To examine the substituent effect at the C-3 and -10 positions of 5-deazaflavo-



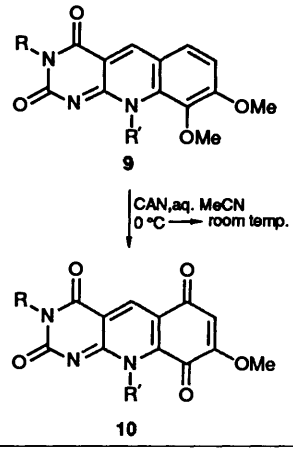
Scheme 2 *Reagents and conditions:* i, DMF, reflux, 4 h; ii, CAN (5 mol equiv.), aq. MeCN, 0 °C→room temp.

Table 1 Synthesis of 8,9-dimethoxy-5-deazaflavins **9**



9	R	R'	Yield (%)
a	H	C_6H_{13}	58
b	H	C_8H_{17}	63
c	H	$C_{12}H_{25}$	74
d	Me	C_6H_{13}	72
e	Me	C_8H_{17}	85
f	Me	$C_{12}H_{25}$	76
g	Ph	C_6H_{13}	68
h	Ph	C_8H_{17}	75
i	Ph	$C_{12}H_{25}$	69

Table 2 8-Methoxy-5-deazaflavo-6,9-quinones **10**



10	R	R'	Yield (%)
a	H	C_6H_{13}	10
b	H	C_8H_{17}	8
c	H	$C_{12}H_{25}$	12
d	Me	C_6H_{13}	28
e	Me	C_8H_{17}	22
f	Me	$C_{12}H_{25}$	24
g	Ph	C_6H_{13}	27
h	Ph	C_8H_{17}	25
i	Ph	$C_{12}H_{25}$	26

6,9-quinones on the amine oxidation, and especially to investigate the effect of lipophilicity on the power of oxidation, several 5-deazaflavo-6,9-quinone derivatives **10** having various side-chains at C-3 and -10 were synthesized (Tables 1 and 2).

Table 3 shows the results of the oxidation of benzylamine with compounds **10**. For comparative purposes, 5-deazaflavin, 3-methyl-10-hexyl-8,9-dimethyl-5-deazaflavin, and 1,4-benzoquinone derivatives were used to oxidize the amine under the same conditions. The relationship between the oxidizing power and the side-chains at C-3 and -10 was vague, but it was interesting that all of the 5-deazaflavo-6,9-quinones have been found to have stronger oxidizing power than the 5-deazaflavins used before[8] and to show autorecycling oxidizing abilities (Table 3).

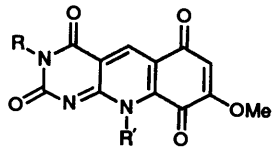
These facts suggest that 5-deazaflavo-6,9-quinones have gained their oxidizing power from the 5-deazaflavin moiety, and their smooth electron-transferring ability from the 1,4-benzoquinone moiety. A proposed mechanism for the autorecycling amine oxidation by 5-deazaflavo-6,9-quinones is illustrated as follows. Firstly, the usual hydride abstraction or an equivalent reaction from the amine would occur at the 5-position of the 5-deazaflavo-6,9-quinone, followed by smooth electron transfer to give a 6,9-dihydroxy-5-deazaflavin **14** (which has not yet been isolated) *via* presumable intermediates **12** and **13**, and finally the diol **14** would be reoxidized by air to the starting 5-deazaflavo-6,9-quinone **11** (Scheme 3).

Experimental

All materials not explicitly discussed were purchased from Wakenyaku Co., Nacalai Tesque Co., and Aldrich Chemical Co. ^{1}H NMR spectra were obtained with a JEOL JNM-FX-200 Fourier transform spectrometer, and *J* values are given in Hz. IR spectra were measured with a Shimadzu IR 400 spectrometer. M.p.s were taken using a Yanagimoto micro-melting point apparatus and are uncorrected. Gas liquid chromatography (GLC) was performed on a Shimadzu GC-7AG with a glass column (2.0 m) packed with 5% free fatty acid phase (FFAP).

Synthesis of 10-*Butyl*-9-*methoxy*-3-*methyl*-5-*deazaflavin* **3**.—A suspension of 6-butylamino-3-methyluracil **1** (800 mg, 4.2 mmol) and 2,3-dimethoxybenzaldehyde **2** (940 mg, 1.4 mol equiv.) in DMF (2 cm^3) was heated for 4 h. Crystals formed after the mixture had cooled were filtered off and recrystallized from ethanol to give *compound* **3** (900 mg, 70%), m.p. > 300 °C;

Table 3 Oxidation of benzylamine with 5-deazaflavo-6,9-quinones and other compounds (conditions; 50% aq. benzylamine solution, ambient air. Reaction time; 40 h. Reaction temp.; 60 °C).



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Compounds **10**	R	R'	Yield (%)[a]	Other compounds	Yield (%)[a]
a	H	C_6H_{13}	144	**9d**	11
b	H	C_8H_{17}	132		
c	H	$C_{12}H_{25}$	104	1,4-Benzoquinone	55
d	Me	C_6H_{13}	183		
e	Me	C_8H_{17}	606	1,4-Naphthoquinone	81
f	Me	$C_{12}H_{25}$	262		
g	Ph	C_6H_{13}	247	None	0
h	Ph	C_8H_{17}	776		
i	Ph	$C_{12}H_{25}$	330		

[a] Based on initial amount of substrate (compounds **10** and other compounds).

Table 4

Compound	R	R'	M.p. (°C)	δ_H(CDCl$_3$) 5-H	6-H	7-H
9a	H	C_6H_{13}	243	8.77	7.20 (*J* 9.0)[a]	7.68
9b	H	C_8H_{17}	232	8.70	7.18 (*J* 9.0)[a]	7.66
9c	H	$C_{12}H_{25}$	225	8.71	7.18 (*J* 8.9)[a]	7.67
9d	Me	C_6H_{13}	221	8.73	7.16 (*J* 8.9)[a]	7.65
9e	Me	C_8H_{17}	216	8.73	7.17 (*J* 9.0)[a]	7.63
9f	Me	$C_{12}H_{25}$	201	8.73	7.17 (*J* 8.9)[a]	7.65
9g	Ph	C_6H_{13}	248	8.76	7.18 (*J* 8.9)[a]	7.66
9h	Ph	C_8H_{17}	199	8.77	7.20 (*J* 9.0)[a]	7.68
9i	Ph	$C_{12}H_{25}$	182	8.77	7.18 (*J* 8.9)[a]	7.65

[a] Coupling constant of 6-H and 7-H of species **9**.

Table 5

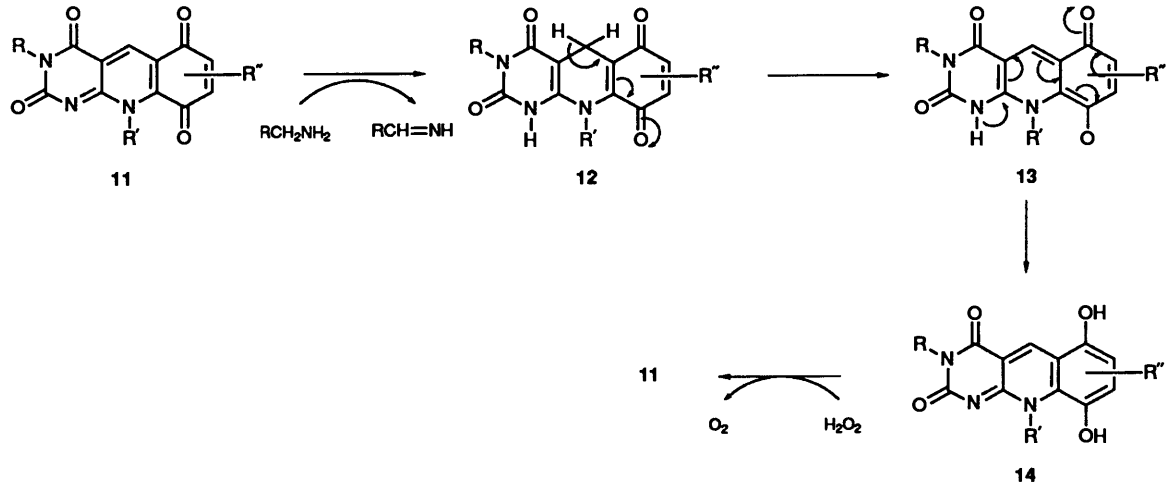
Compound	Formula	Anal. calc./Found (%) C	H	N
9a	$C_{19}H_{23}N_3O_4$	63.9	6.4	11.8
		63.6	6.4	11.5
9b	$C_{21}H_{27}N_3O_4$	65.45	7.0	10.9
		65.7	7.1	10.9
9c	$C_{25}H_{35}N_3O_4$	70.6	8.2	9.9
		70.3	8.3	9.75
9d	$C_{20}H_{25}N_3O_4 \cdot 1/2H_2O$	63.15	6.8	11.05
		63.6	6.7	11.0
9e	$C_{22}H_{29}N_3O_4$	66.2	7.3	10.5
		66.1	7.2	10.5
9f	$C_{26}H_{37}N_3O_4$	68.6	8.1	9.2
		68.35	8.2	9.2
9g	$C_{25}H_{27}N_3O_4$	69.3	6.2	9.7
		69.4	6.3	9.7
9h	$C_{27}H_{31}N_3O_4$	70.3	6.7	9.1
		70.3	6.7	9.1
9i	$C_{31}H_{39}N_3O_4$	71.95	7.5	8.1
		72.0	7.7	8.1

Table 6

Compounds	R	R'	δ_H(CDCl$_3$) 5-H	7-H
10a	H	C_6H_{13}	8.95	6.18
10b	H	C_8H_{17}	8.94	6.18
10c	H	$C_{12}H_{25}$	8.94	6.19
10d	Me	C_6H_{13}	9.09	6.21
10e	Me	C_8H_{17}	9.09	6.21
10f	Me	$C_{12}H_{25}$	9.10	6.22
10g	Ph	C_6H_{13}	9.10	6.20
10h	Ph	C_8H_{17}	9.12	6.21
10i	Ph	$C_{12}H_{25}$	9.12	6.21

δ_H(200 MHz; CDCl$_3$) 8.83 (1 H, s), 7.48 (1 H, dd, *J* 2.2 and 7.3), 7.41 (1 H, dd, *J* 7.3 and 7.6), 7.34 (1 H, dd, *J* 2.2 and 7.6), 4.03 (3 H, s), 3.47 (3 H, s), 0.98 (3 H, t, *J* 7.3) (Found: C, 63.3; H, 5.9; N, 13.1. $C_{17}H_{19}N_3O_3 \cdot 1/2H_2O$ requires C, 63.35; H, 6.2; N, 13.0%).

10-*Butyl*-3-*methyl*-5-*deazaflavo*-6,9-*quinone* **4**.—To a suspension of the 9-methoxy-5-deazaflavin **3** (100 mg) in MeCN (5 cm^3) at 0 °C was added slowly aqueous CAN (2.2 g in 5 cm^3).



Scheme 3 Proposed redox mechanism for 5-deazaflavo-6,9-quinones

Table 7

Compounds	Formula	M.p. (°C)	Anal. calc./Found (%) C	H	N
10a	$C_{18}H_{19}N_3O_5$	170	60.5	5.3	11.8
			60.25	5.2	12.0
10b	$C_{20}H_{23}N_3O_5$	162	62.3	6.0	10.9
			62.3	5.95	10.65
10c	$C_{24}H_{31}N_3O_5$	184	65.3	7.0	9.5
			65.3	7.0	9.4
10d	$C_{19}H_{21}N_3O_5 \cdot 1/2H_2O$	210	60.0	5.8	11.05
			60.3	5.7	11.1
10e	$C_{21}H_{25}N_3O_5$	165	63.2	6.3	10.5
			62.8	6.4	10.2
10f	$C_{25}H_{33}N_3O_5$	192	65.9	7.25	9.2
			65.4	7.2	8.9
10g	$C_{24}H_{23}N_3O_5$	180	66.5	5.3	9.7
			66.2	5.4	9.7
10h	$C_{26}H_{27}N_3O_5 \cdot 1/2H_2O$	194	66.4	5.95	8.9
			66.5	5.9	9.0
10i	$C_{30}H_{35}N_3O_5$	185	69.6	6.75	8.0
			69.4	6.75	8.0

The reaction mixture was stirred at room temperature for 2 h and then was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4 and evaporated under reduced pressure without heating. The residue was purified by silica gel column chromatography to give *compound* **4** (35%), m.p. 200 °C (decomp.); δ_H(200 MHz; $CDCl_3$) 9.09 (1 H, s), 7.06 (2 H, s), 5.0 (2 H, m), 3.45 (3 H, s), 1.58 (4 H, m) and 1.01 (3 H, t, *J* 7.2) (Found: C, 61.5; H, 4.9; N, 13.3. $C_{16}H_{15}N_3O_4$ requires C, 61.3; H, 4.8; N, 13.4%).

Synthesis of 10-*Butyl*-8,9-*dimethoxy*-3-*methyl*-5-*deazaflavin* **6**.—A suspension of 6-butylamino-3-methyluracil **1** (900 mg, 4.6 mmol) and 2,3,4-trimethoxybenzaldehyde **5** (1.26 g, 1.4 mol equiv.) in DMF (2 cm^3) was heated for 4 h. Crystals obtained after the mixture had cooled were filtered off and recrystallized from EtOH to give *compound* **6** (1.0 g, 64%), m.p. > 300 °C; δ_H(200 MHz; $CDCl_3$) 8.73 (1 H, s), 7.65 (1 H, d, *J* 8.8), 7.18 (1 H, d, *J* 8.8), 4.08 (3 H, s), 3.92 (3 H, s), 3.46 (3 H, s) and 0.94 (3 H, t, *J* 7.3) (Found: C, 62.3; H, 6.2; N, 12.8. $C_{18}H_{21}N_3O_4$ requires C, 62.95; H, 6.2; N, 12.2%).

10-*Butyl*-8-*methoxy*-3-*methyl*-5-*deazaflavo*-6,9-*quinone* **7**.—To a suspension of the 8,9-dimethoxy-5-deazaflavin **6** (200 mg) in MeCN (10 cm^3) at 0 °C was slowly added aqueous CAN (3.5 g in 6 cm^3). The reaction mixture was then stirred at room temperature for 2 h before being extracted with CH_2Cl_2, and the extract was dried with Na_2SO_4 and the solvent was evaporated off under reduced pressure without heating. The residue was purified by silica gel column chromatography (26%), δ_H(200 MHz; $CDCl_3$) 9.12 (1 H, s), 6.21 (1 H, s), 3.96 (3 H, s), 3.46 (3 H, s) and 1.01 (3 H, dd, *J* 7.5 and 7.1) (Found: C, 58.9; H, 5.1; N, 11.7. $C_{17}H_{17}N_3O_5 \cdot 1/4H_2O$ requires C, 58.7; H, 5.0; N, 12.1%).

8,9-*Dimethoxy*-5-*deazaflavins* **9a–9i**.—*General procedure.* A suspension of a 6-aminouracil **8** (5 mmol) and 2,3,4-trimethoxybenzaldehyde **5** (5.5 mmol) in DMF (2 cm^3) was heated for 4 h. The crystalline product was filtered off, and recrystallized from EtOH. Analytical and spectral data are shown in Tables 4 and 5.

General Procedure for 5-*Deazaflavo*-6,9-*quinones* **10a–10i** *by CAN Oxidation.*—To a suspension of a 8,9-dimethoxy-5-deazaflavin **9** (2 mmol) in MeCN (10 cm^3) at 0 °C was slowly added CAN (5.5 mol equiv. in 6 cm^3). The reaction mixture was stirred at room temperature overnight before being extracted with CH_2Cl_2, and the extract was then dried with Na_2SO_4 and then evaporated under reduced pressure without heating. The residue was purified by silica gel column chromatography [4.0 cm × 20 cm; $CHCl_3$–acetone (6:1) as developing solvent]. Analytical and spectral data are shown in Tables 6 and 7.

Oxidation of Benzylamine with 5-*Deazaflavo*-6,9-*quinones* **10**.—A 5-deazaflavo-6,9-quinone **10** (0.1 mmol) and aq. benzylamine (benzylamine–water 1:1) (5 cm^3) were mixed at 60 °C for 40 h in air. The reaction mixture was then treated with 5% HCl and extracted with chloroform. Benzaldehyde thus obtained was measured by GLC. The results are shown in Table 3.

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Paper 2/05714J
Received 26*th October* 1992
Accepted 30*th November* 1992