The Autorecycling Oxidation of Benzylamine by Synthetic 8-Hydroxy-5-deazaflavin Derivatives

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Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

Various 8-hydroxy-5-deazaflavin derivatives were synthesized as the model compounds of coenzyme F_{420}. These compounds oxidized benzylamine to benzaldehyde more efficiently than the corresponding 8-unsubstituted 5-deazaflavins.

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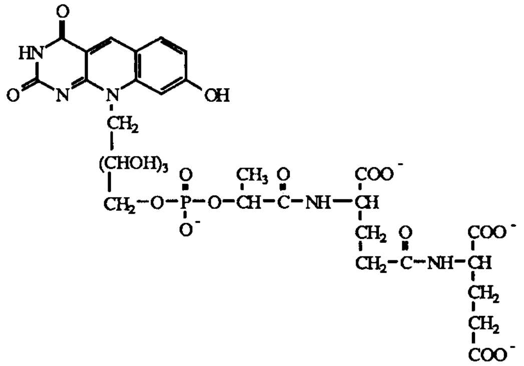
In 1978, the coenzyme factor 420 (F_{420}) (**1**) was isolated from methane producing bacteria and has been found to function as the low potential electron carrier in the reduction of CO_2 to CH_4 [1]. F_{420} has 8-hydroxy-5-deazaflavin skeleton in the molecule (Scheme 1) and its first total synthesis has recently been achieved in this laboratory [2]. Prior to the discovery of F_{420}, we had been engaged in the biofunctional chemistry of 5-deazaflavins and related compounds as flavin or NAD models [3,4], and found that they acted as autorecycling redox turnover catalysts [5-8]. These are the first examples for the autorecycling reactions using the synthetic organic catalysts. For instance we reported the autorecycling oxidation of several amines by a simple 5-deazaflavin [6]. In the present paper we describe the synthesis of 8-hydroxy-5-deazaflavin derivatives as the model compounds of F_{420} and the autorecycling oxidation of benzylamine using them.

Scheme 1



Syntheses of 8-Hydroxy-5-deazaflavin Derivatives.

The 8-hydroxy-5-deazaflavin derivatives have been synthesized according to the known two procedures developed by us [9,10]. In the first place, 6-chloro-5-formyluracils [9] and *N*-alkyl-*m*-aminophenols **2a-f** were refluxed in *N*,*N*-dimethylformamide (DMF) to give the corresponding 8-hydroxy-5-deazaflavins **3a-1** in fairly good yields [9] (Table 2). The starting materials **2a-f** were prepared by the usual alkylation of *m*-aminophenol with the corresponding alkyl bromides (Table 1).

In the next place, we synthesized the 8-hydroxy-5-deazaflavins having a carboxylic function in the N-10 side chain by another route [10]. Thus, 6-chloro-3-methyluracil and γ-amino-*n*-butyric acid or ϵ-amino-*n*-caproic acid were fused to give the corresponding 6-(substituted amino)uracils **4a,b**. Then compounds **4a,b** were condensed with 2-chloro-4-hydroxybenzaldehyde in DMF under reflux to yield (8-hydroxy-3-methyl-5-deazaflavin-10-yl)butyric acid (**5a**) and (8-hydroxy-3-methyl-5-deazaflavin-10-yl)caproic acid (**5b**) (Table 3).

The 8-hydroxy-5-deazaflavins **3** and **5** thus obtained showed characteristic C(5)-proton signals in low field [δ 9.50-9.66 ppm (trifluoroacetic acid)] in ^1H nmr spectra.

Oxidation of Benzylamine using 8-Hydroxy-5-deazaflavins.

The 8-hydroxy-5-deazaflavins **3** oxidized benzylamine to give benzaldehyde (isolated as 2,4-dinitrophenylhydrazone) by the treatment of the reaction mixture with hydrochloric acid solution of 2,4-dinitrophenylhydrazine. In every reaction, a considerable high autorecycling was observed and the yield of benzaldehyde reached more than 1000% after 10 hours at 90°. This means that the oxidative ability of compounds **3** are superior to that of simple 5-deazaflavin already reported [6]. In this connection, Shinkai *et al.* reported the alcohol oxidation by 3-hydroxy-*N*-methylacridinium under strong basic condition, in which the presence of 3-hydroxyl group is essential for the appearance of the oxidation [11]. The fact that the presence of 8-hydroxyl group in the 5-deazaflavin nucleus enhanced the oxidative ability toward benzylamine seemed

Table 1
Synthesis of *N*-Alkyl-*m*-aminophenols **2**

Compound	R	Yield (%)	Bp	Formula	Analysis (%) Cacld./Found		
					C	H	N
2 a	CH_3	65	146°C/14 mm Hg	C_7H_9NO	68.27 68.49	7.37 7.48	11.37 11.06
2 b	C_2H_5	85	138°C/8 mm Hg	$C_8H_{11}NO$	70.04 70.23	8.08 8.21	10.21 10.02
2 c	C_4H_9	62	146°C/5 mm Hg	$C_{10}H_{15}NO$	72.69 72.83	9.15 9.24	8.48 8.09
2 d	C_6H_{13}	47	168°C/5 mm Hg	$C_{12}H_{19}NO$	74.57 74.68	9.91 10.12	7.25 7.02
2 e	C_8H_{17}	54	205°C/6 mm Hg	$C_{14}H_{23}NO$	75.97 76.12	10.47 10.58	6.33 6.10
2 f	$C_{12}H_{25}$	51	205°C/4 mm Hg	$C_{18}H_{31}NO$	77.92 78.14	11.26 11.33	5.05 4.98

Scheme 2

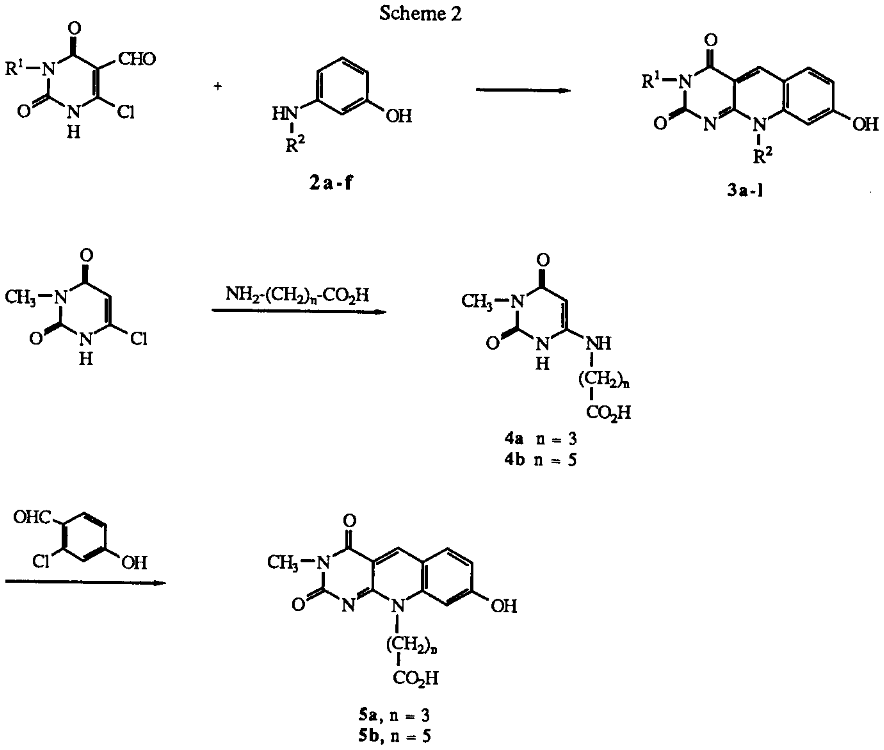


Table 2

Synthesis of 8-hydroxy-5-deazaflavins **3**

Compound	R_1	R_2	Yield (%)	Mp	Formula	Analysis (%) Cacld./Found		
						C	H	N
3 a	CH_3	CH_3	40	>350	$C_{13}H_{11}N_3O_3$	60.69	4.31	16.34
						60.97	4.37	16.17
3 b	CH_3	C_2H_5	55	>350	$C_{14}H_{13}N_3O_3$	61.98	4.83	15.49
						61.96	5.03	15.43
3 c	CH_3	C_4H_9	38	>350	$C_{16}H_{17}N_3O_3$	64.20	5.72	14.04
						64.12	5.75	13.87
3 d	CH_3	C_6H_{13}	50	312	$C_{18}H_{21}N_3O_3$	66.03	6.47	12.84
						66.20	6.50	12.61
3 e	CH_3	C_8H_{17}	40	310	$C_{20}H_{25}N_3O_3$	67.58	7.09	11.82
						67.43	6.97	11.69
3 f	CH_3	$C_{12}H_{25}$	42	253	$C_{24}H_{33}N_3O_3$	70.04	8.08	10.21
						69.92	8.00	10.11
3 g	C_6H_5	CH_3	54	>350	$C_{18}H_{13}N_3O_3$	67.70	4.11	13.16
						67.52	4.07	13.04
3 h	C_6H_5	C_2H_5	70	>350	$C_{19}H_{15}N_3O_3$	68.46	4.54	12.61
						68.76	4.52	12.71
3 i	C_6H_5	C_4H_9	60	>350	$C_{21}H_{19}N_3O_3$	68.75	5.48	12.03
						69.05	5.28	11.76
3 j	C_6H_5	C_6H_{13}	74	341	$C_{23}H_{23}N_3O_3$	70.93	5.95	10.79
						70.54	5.89	10.62
3 k	C_6H_5	C_8H_{17}	65	334	$C_{25}H_{27}N_3O_3$	71.92	6.52	10.07
						71.81	6.56	10.07
3 l	C_6H_5	$C_{12}H_{25}$	70	293	$C_{29}H_{35}N_3O_3$	73.54	7.54	8.87
						73.31	7.51	8.81

Scheme 3

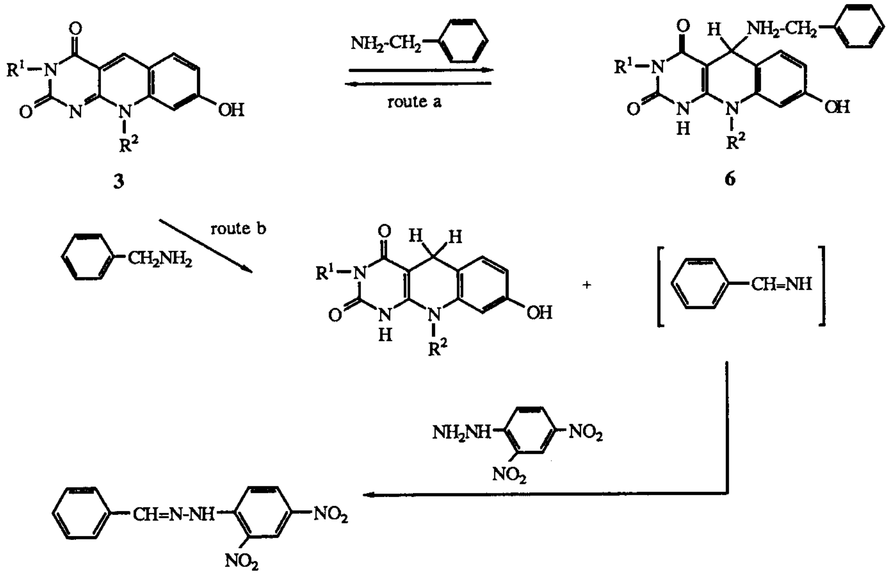


Table 3

Synthesis of 8-hydroxy-5-deazaflavins **5**

Compound	Yield (%)	Mp (°C)	Formula	Analysis (%) Cacld./Found		
				C	H	N
5 a	36.5	>300	$C_{16}H_{15}N_3O_5 \cdot 1/3H_2O$	57.36 57.16	4.71 4.51	12.54 12.28
5 b	35.5	>300	$C_{18}H_{19}N_3O_5$	60.49 60.19	5.36 5.35	11.76 11.67

Table 4

Oxidation of Benzylamine by 8-hydroxy-5-deazaflavins **3** [a]

Compound	Yield (%) [b]	
	(based on deazafavins)	(based on benzylamine)
3 a	1637	16.2
3 b	3486	26.2
3 c	3965	28.4
3 d	3935	25.0
3 e	3965	25.4
3 f	5856	27.5
3 g	2617	16.4
3 h	3697	20.8
3 i	3195	22.0
3 j	4289	22.4
3 k	5431	29.8
3 l	5950	26.0

[a] Reaction conditions: 90°, 10 hours.

[b] Isolated as the 2,4-dinitrophenylhyrazone.

to be the case similar to the oxidation by *N*-methylacridinium.

As for the reaction mechanism, it is considered that there are two competitive pathways in the above oxidation of benzylamine (Scheme 3). One is the reversible addition of benzylamine into the 5 position of 5-deazaflavins (route a), and the other is the irreversible hydride or its equivalent transfer route (route b). In the former route, the adducts **6** are rather unstable because of the electron releasing effect by 8-hydroxyl group, therefore the hydride transfer reaction by route b would be significantly enhanced to give the higher yields of benzaldehyde.

Table 4 also shows the relationship between the structure of 5-deazaflavins and their oxidative ability toward benzylamine. In general, the longer the alkyl side chain at N-10 becomes, the more the autorecycling oxidation becomes efficient. Table 5 shows the dependency of the oxidation using 8-hydroxy-10-lauryl-3-phenyl-5-deazaflavin (**3l**) upon the time and temperature. It should be noted that the oxidation by **3l** for 50 hours at 90° gave 87%

yield of benzaldehyde based on the starting benzylamine (16500% yield based on the 5-deazaflavin catalyst).

The 8-hydroxy-5-deazaflavins **5a,b** having the carboxylic side chain did not show any appreciable oxidizing ability toward benzylamine.

Table 5

Time and Temperature Dependence in the Oxidation of Benzylamine by Compound **31**

Reaction Condition		Yield (%) [a]	
Temperature (C°)	Time (h)		
10-20	20	trace	
60	20	2273[b]	9.4[c]
90	10	5950	26
90	50	16512	87
120	10	12196	46

[a] Isolated as 2.4-dinitrophenylhydrazone.

[b] Based on compound **31.**

[c] Based on benzylamine.

EXPERIMENTAL

All melting points were determined on a Yanagimoto hot-stage apparatus, and are uncorrected. The ^{1}H nmr spectra were obtained on a JEOL-PMX 60 spectrometer.

N-Methyl- (**2a**) and *N*-Ethyl-*m*-aminophenol (**2b**).

A mixture of *m*-aminophenol (4.0 g, 37 mmoles) and methyl iodide (5.1 g, 37 mmoles) for **2a** or ethyl iodide (5.6 g, 37 mmoles) for **2b** was heated in DMF (20 ml) in the presence of potassium carbonate (5.0 g, 37 mmoles) for 2 hours at 100°. The reaction mixture was evaporated under reduced pressure, the residue was diluted with water and the solution was extracted with ether. After ether was removed, the residue was distilled under reduced pressure to give compounds **2a** and **2b** (Table 1).

N-Alkyl-*m*-aminophenols **2c-f**. General Procedure.

A mixture of *m*-aminophenol (4.0 g, 37 mmoles) and alkyl bromides (37 mmoles) was fused for 3 hours at 120°. To the reaction mixture 10% potassium carbonate solution (50 ml) was added and the solution was extracted with ether. The ether extracts were evaporated and the residue was distilled under reduced pressure to give the corresponding *N*-alkyl-*m*-aminophenols (Table 1).

8-Hydroxy-5-deazaflavins **3a-f**. General Procedure.

A mixture of 6-chloro-5-formyl-3-methyluracil (1.0 g, 5.3 mmoles) and *N*-alkyl-*m*-aminophenol **2a-f** was heated in DMF (10 ml) under reflux for 1 hour. Yellow precipitate was filtered off and recrystallized from acetic acid or ethanol (Table 2).

8-Hydroxy-5-deazaflavins **3g-l**. General Procedure.

6-Chloro-5-formyl-3-phenyluracil (1.0 g, 3.9 mmoles) and *N*-alkyl-*m*-aminophenol **2a-f** were heated in DMF (10 ml) under reflux for 3 hours. After DMF was removed, the product was crystallized from water and recrystallized from DMF or ethanol (Table 2).

3-Methyl-6-(substituted amino)uracils **4a,b**.

According to the known procedure [12], 6-chloro-3-methyluracil and γ-amino-*n*-butyric acid for **4a** or ϵ-amino-*n*-caproic acid for **4b** were fused for 1 hour to give the corresponding 3-methyl-6-(substituted amino)uracils **4a,b**.

Compound **4a**.

This compound was obtained in 23% yield, mp 222-225°; ms: m/e 227 (M^+).

Anal. Calcd. for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.34; H, 5.79; N, 18.50.

Compound **4b**.

This compound was obtained in 53% yield, mp 221-224°; ms: m/e 255 (M^+).

Anal. Calcd. for $C_{11}H_{17}N_3O_4$: C, 51.75; H, 6.71; N, 16.46. Found: C, 51.57; H, 6.57; N, 16.34.

8-Hydroxy-5-deazaflavins **5a,b**. General Procedure.

Compounds **4a,b** (1.0 mmole) and 2-chloro-4-hydroxybenzaldehyde (1.2 mmoles) [13] were refluxed in DMF (2.5 ml) for 3-5 hours. To the reaction mixture ethanol (10 ml) was added and the precipitate was filtered off and recrystallized from DMF.

Oxidation of Benzylamine by 8-Hydroxy-5-deazaflavins. General Procedure.

Benzylamine solution (2.0 g, 18.6 mmoles) containing 8-hydroxy-5-deazaflavins **3a-l** (20 mg) was heated at 90° for 10 hours. The reaction mixture was diluted with ether (10 ml) and then 2*N* hydrochloric acid solution of 2,4-dinitrophenylhydrazine was added to the solution. Benzaldehyde 2,4-dinitrophenylhydrazone as yellow precipitate was filtered off, dried and weighed (Table 4).

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