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Porphyrins Coupled with Nucleoside Bases. Synthesis and Characterization of Adenine- and Thymine-Porphyrin Derivatives

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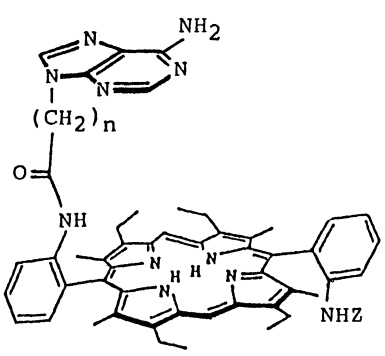
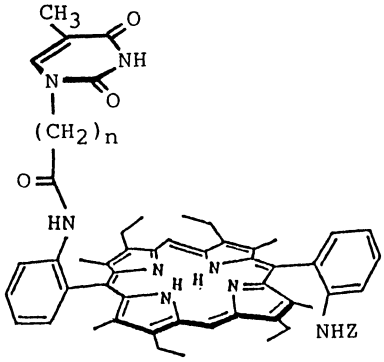
Several porphyrins linked to an adenine or thymine have been synthesized. Spectroscopic study suggested an interaction between the porphyrin ring and the base moiety, and indicated nucleoside base recognition ability of the compounds.

Several interesting compounds containing a nucleoside base pair were synthesized and their functions were investigated.[1] On the other hand, an unusually great affinity of porphyrin derivatives and metalloporphyrins for nucleic acids or nucleoside base was shown by spectroscopic and kinetic studies.[2] In this letter,[3] we describe synthesis and spectroscopic characterization of several porphyrin derivatives (**1**-**4**) coupled with an adenine or thymine, which may be available as model compounds to fundamental investigation of the interaction between porphyrins and nucleoside bases. A porphyrin having an guanine-cytosine pair was recently presented by Sessler et al.,[4] but its structural situation is different from our compounds.

Some methods were attempted to connect nucleoside base moieties to porphyrin. Reaction of adenine-9-alkanoic acids (**5d** and **6d**) and trans-bis(o-aminophenyl)tetraethyltetramethylporphyrin (**9a**)[5] with dicyclocarbadiimide (DCC) in dimethylformamide (DMF) in the presence of pyridinium chloride (Py.HCl) gave coupling products **1a** and **2a**, respectively, but only in very low yields (2-5%). Porphyrin **9a** and base **5d-8d** were treated with $ClCO_2Et$/Py.HCl in DMF and tetrahydrofuran (THF) to afford the corresponding carbamate derivatives **1b**, **2b**, **3b**, and **4b** in relatively good yields (11-41%). Then, porphyrin **9b** prepared from **9a** by protecting one of the amino groups with carbobenzyloxy (CBZ) group was used. Reaction of **9b** and alkanoic acids **5d-8d** with $ClCO_2Et$/Py.HCl in DMF/THF afforded the corresponding coupling products **1c**, **2c**, **3c**, and **4c** (11-23%). The CBZ groups of **1c** and **2c** were removed by catalytic hydrogenation with Pd-C in ethanol/HCl

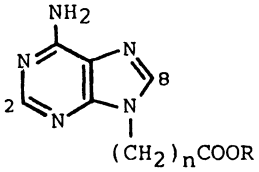


1 : n=3 **2** : n=4

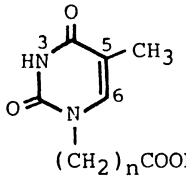


3: n=3 **4**: n=4

a : Z=H
b : Z=$COOC_2H_5$
c : Z=$COOCH_2C_6H_5$



5: n=3 **6**: n=4



7: n=3 **8**: n=4

d : R=H
e : R=C_2H_5

to give **1a** and **2a** (ca. 60%), respectively.

The mass spectra of all products measured by field-desorption ionizing method showed the base peaks at m/z value corresponded to the molecular ion peak, and their structures were confirmed by NMR spectrometry. The assignments of the signals were determined by HH-COSY and HC-COSY techniques. Adenine, thymine and N-methylene protons of all derivatives shifted to fairly high fields compared with those of the corresponding alkanoates **5e**-**8e** (Table 1). Those high field shifts should be caused by the ring current anisotropic effect of porphyrin ring, and indicate that the adenine and thymine moieties are located at an upper zone of porphyrin ring. Furthermore, the proton signals of the base linked to porphyrin moiety with a trimethylene chain (n=3) shift to higher fields than those with a tetramethylene chain (n=4), except for the 6-proton of **4**. The electronic spectra of the compounds showed a hypochromic effect of the Soret band (407-410 nm) of porphyrin, and decrease of molar extinction coefficient in trimethylene compounds **1b** and **3b** (20-30%) was large in comparison with those of tetramethylene compounds **2b** and **4b** (ca. 10%). Therefore, the base moieties of the formers are nearer to the porphyrin ring than those of the latters. Inspection with a CPK molecular model supports the above assumption. Deviation of the 6-proton of **4** from the behavior of the other protons would be caused by difference of conformation from the others.

Molecular recognition of nucleoside bases with various artificial receptors has been studied by many chemists.[6] Our compounds having a nucleoside base in the upper zone of porphyrin ring could recognize the other nucleoside base in forming base pair and the recognition was detected

Table 1. ^{1}H-NMR spectral data (in $CDCl_3$, 500 MHz, in δ) of nucleoside base-butanoate (**5-8**) and nucleoside base-porphyrin derivatives (**1-4**)

Compd	Adenine moiety			Thymine moiety			Side-arm methylene-H[b]			
	2,8-H[a]		-NH_2	3-NH	5-CH_3	6-H				
5	7.81	8.36	5.75				4.29	2.23		2.35
6	7.80	8.36	5.73				4.22	1.96	1.67	2.36
7				8.60	1.93	7.02	3.77	2.01		2.38
8				8.55	1.93	6.98	3.71	1.73	1.67	2.36
1a	6.41	6.72	4.44				2.75	1.35		1.51
1b	6.44	6.71	4.40				2.76	1.37		1.55
1c	6.44	6.72	4.42				2.76	1.38		1.53
2a	6.96	7.96	5.41				3.19	0.80	1.07	1.33
2b	7.02	7.95	5.35				3.25	0.86	1.12	1.37
2c	7.02	7.96	5.35				3.25	0.85	1.11	1.35
3b				6.88	1.20	6.05	2.69	1.25		1.36
3c				6.82	1.00	5.83	2.56	1.20		1.32
4b				7.50	1.37	5.78	2.65	0.80	0.80	1.38
4c				7.63	1.35	5.71	2.60	0.77	0.77	1.37

a) The assignments of the signals to 2-H and 8-H were not clear.
b) The chemical shifts of the signals are described in the order of N-CH_2-CH_2-(CH_2)-CH_2-CO.

Table 2. Variation of chemical shift differences (Δδ)[a] of thymine- and adenine-butanoate when being mixed with adenine- and thymine-porphyrin derivatives, respectively

Por. deriv.	Ester	Concn of Por./M	Th/Ad[b]	Adenine moiety			Thymine moiety		
				-NH_2	2-H or 8-H		3-NH	5-CH_3	6-H
1b	**7e**	0.05	0.5	+0.52[c]			+2.20	-0.11	-0.23
1b	**7e**	0.01	0.3	+0.15[c]			+1.01	-0.07	-0.11
1b	**7e**	0.01	1.0	+0.38[c]			+0.87	-0.06	-0.10
1b	**7e**	0.01	3.0	+0.78[c]			+0.77	-0.05	-0.08
2b	**7e**	0.01	3.0	+0.77[c]			+0.75	-0.03	-0.04
3b	**5e**	0.05	2.0	+0.26	-0.21	-0.18	+2.66[c]		
3b	**5e**	0.01	2.0	+0.28	-0.06	-0.06	+1.08[c]		

a) Chemical shift differences from the corresponding proton shifts of each compound in a separate measurement. b) Mole ratio of thymine and adenine. c) Shift of proton signal in porphyrin derivative.

by ^{1}H-NMR spectrometry. When solution of **7e** in $CDCl_3$ was treated with **1b**, sizable down field shifts of the 3-NH of **7e** and the amino protons of **1b** and upfield shifts in the 5-CH_3 and 6-H of **7e** were observed (Table 2). There were only little changes in the ester ethyl protons of **7e** (ca. 0.01 ppm) and the adenine protons of **1b** (ca. 0.05 ppm). The shifts were varied with concentration and thymine/adenine mole ratio. When **2b** having a longer side methylene chain than **1b** was used as a receptor, the shift differences in the amino protons of adenine and the 3-NH of **7e** were almost similar to the case of **1b** but those in the other protons decrease. In the combination of thymine-porphyrin **3b** and adenine-butanoate **5e**, a similar shift behavior was also observed. Those results indicate that a base pairing with hydrogen bonding occurs between two base moieties in the upper zone of the porphyrin ring.

Synthesis of porphyrin derivatives having guanine, cytosine, adenine-thymine pair or guanine-cytosine pair are in progress.

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