

Eilatin: Semiempirical MO Calculations of Molecular Structures and Electronic Spectra of the Unprotonated and *N*-Protonated Molecules

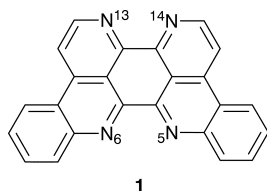
Tsuguo Sato* and Masahiro Kataoka*

Tohoku College of Pharmacy, Komatsushima 4-4-1, Aoba-ku, Sendai 981-8558, Japan

J. Chem. Research (S),
1998, 542–543
J. Chem. Research (M),
1998, 2451–2464

The molecular structures and electronic spectra of eilatin and protonated eilatin molecules have been investigated in terms of AM1 and CNDO/S methods, the calculated electronic spectra of free and monoprotonated eilatin molecules being in good agreement with the electronic spectra of eilatin observed in non-acidic and acidic media.

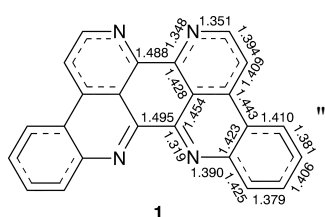
Eilatin (C₂₄H₁₂N₄) (**1**), a fused heptacyclic aromatic marine alkaloid having a novel unique highly symmetric structure, has been isolated from the Red Sea tunicate *Eudistoma* sp. first by Rudi and Kashman.¹ This molecule is currently of great interest^{2–5} because of its significant biological activities.² The bioactivities motivate chemists to synthesize eilatin.^{3,4} Rudi and Kashman have made an X-ray structural analysis of eilatin^{1a} and also reported the electronic spectra of eilatin in non-acidic and acidic media.¹ However, no detailed structural information such as bond lengths has been reported, and no interpretation of the electronic spectra of eilatin in non-acid and acid media has been made, either. These factors led us to investigate the molecular structures and electronic spectra of eilatin and protonated eilatin molecules by using AM1^{6,7} and CNDO/S⁸ methods. When calculating the electronic spectra, we used the molecular structures obtained by the AM1 method.



1

The heat of formation of eilatin is calculated to be 178.2 kcal mol⁻¹. Fig. 1 summarizes the C–C and C–N bond lengths of the calculated structure. The results show that eilatin has a planar C_{2v} structure. Eilatin has two long C–C bonds (1.488 and 1.495 Å). This indicates that eilatin may be regarded as a perturbed system of two distinguishable parts, two 3,6-diazaphenanthroline(3,6-DAZPH)-like rings.

The calculated electronic spectrum of eilatin listed in Table 1 predicts that the lowest B₂ transition at 3.32 eV corresponds to the three progression peaks in the range of 2.86–3.20 eV. The observed peak at 3.44 eV should be attributed to the second B₂ and the first A₁ allowed transition (3.66 eV). Moreover, the observed peak at 4.33 eV should be assigned to the second A₁ allowed transition at 4.37 eV. The observed peak at 5.12 eV is predicted to be composed of the fourth A₁ (4.74 eV) and the seventh B₂ (4.98 eV) allowed transition. The observed absorption peaks



1

Fig. 1 Optimized C–C and C–N bond lengths (Å) of eilatin **1**

Table 1 Calculated singlet transition energies (ΔE) and intensities (f) of eilatin with C_{2v} symmetry

Transition symmetry	Theoretical		Experimental ^a ΔE /eV (log ϵ)
	ΔE /eV	f	
B ₂	3.32	0.998 ($\pi \rightarrow \pi^*$)	2.86 (4.43) 3.04 (4.48) 3.20 (4.32) 3.44 ^b (4.06)
B ₂	3.66	0.002 ($\pi \rightarrow \pi^*$)	
A ₁	3.66	0.004 ($\pi \rightarrow \pi^*$)	
B ₁	4.11	0.000 ($n \rightarrow \pi^*$)	
A ₂	4.15	forb. ($n \rightarrow \pi^*$)	
B ₂	4.25	0.005 ($\pi \rightarrow \pi^*$)	
A ₁	4.37	0.289 ($\pi \rightarrow \pi^*$)	4.33 (4.56)
B ₂	4.50	0.009 ($\pi \rightarrow \pi^*$)	
A ₁	4.59	0.060 ($\pi \rightarrow \pi^*$)	
B ₂	4.61	0.000 ($\pi \rightarrow \pi^*$)	
B ₁	4.67	0.000 ($n \rightarrow \pi^*$)	
B ₂	4.70	0.005 ($\pi \rightarrow \pi^*$)	
A ₁	4.74	1.215 ($\pi \rightarrow \pi^*$)	5.12 (4.68)
A ₁	4.83	0.001 ($\pi \rightarrow \pi^*$)	
B ₂	4.98	1.247 ($\pi \rightarrow \pi^*$)	

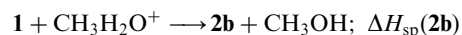
^aRef. 1(b). ^bIn ref. 1(a), the value obtained is 3.39 eV.

can thus be well accounted for by use of the predicted singlet transition of eilatin.

For mono-protonated eilatin molecules, 13- (**2a**) and 6-protonated (**2b**) structures are possible. As listed in Table 2, **2b** is more stable than **2a**.

The optimized C_s structure of **2b** (Fig. 3) has two long C–C bonds (1.486 and 1.484 Å), which suggest that **2b** assumes the geometrical structure formally consisting of 3,6-DAZPH-like and 6-protonated 3,6-DAZPH-like skeletons. This is supported by the localization of positive charge in the 6-protonated 3,6-DAZPH-like region of **2b** (+0.82 *e*).

We then examined the stability of **2b** by using the heat of protonation in a solvated-proton process



Here, we use an oxonium ion,^{1a} CH₃H₂O⁺. ΔH_{sp} (**2b**) is calculated to be –57.7 kcal mol⁻¹. In the presence of H⁺, therefore, the protonation of eilatin readily proceeds to give **2b**.

Table 2 Heat of formation energies (ΔH_f) and relative energies ($\Delta\Delta H_f$) of **2a**, **2b**, **3a–3d**, **4a** and **4b**

Molecule	ΔH_f /kcal mol ⁻¹	$\Delta\Delta H_f$ /kcal mol ⁻¹
2a	317.9	2.0 ^a
2b	315.9	0
3a	544.6	24.1 ^b
3b	544.3	23.8 ^b
3c	524.0	3.5 ^b
3d	520.5	0
4a	815.2	0
4a (C _s)	815.3	0.1 ^c
4b	818.5	3.3 ^c

^aRelative to **2b**. ^bRelative to **3d**. ^cRelative to **4a**.

*To receive any correspondence.

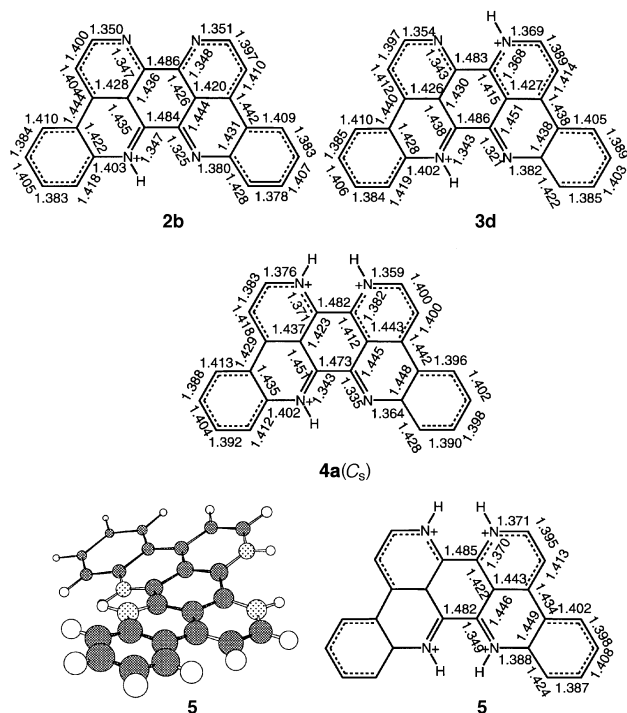


Fig. 3 Optimized C-C and C-N bond lengths (Å) of protonated eilatin molecules **2b**, **3d**, **4a** (C_s) and **5**, and molecular structure (bottom left) of **5**

Table 3 shows the calculated transition energies and intensities of **2b** for comparison with the available experimental data.¹ Our calculation predicts that the first allowed A' transition at 2.76 eV is assigned to the lowest absorption peak observed at 2.82 eV. The observed peak at 4.06 eV corresponds to the sixth A' allowed transition at 4.29 eV.

Diprotonation results in four isomers: 13,14- (**3a**), 5,6- (**3b**), 6,13- (**3c**) and 6,14-diprotinated (**3d**) eilatin molecules. The heats of formation for **3a**–**3d** (Table 2) show that **3d** is the most stable.

Fig. 3 shows the optimized C_s structure of **3d**. Since **3d** has two long C-C bonds (1.483 and 1.486 Å), it can be considered a perturbed system of 3- and 6-protonated 3,6-DAZPH molecules: the calculated ring charges are +1.02 and +0.98 e , respectively.

We next estimated the stabilization energy [ΔH_{sp} (**3d**)] made by the following protonation: **2b** + $\text{CH}_3\text{H}_2\text{O}^+ \rightarrow \text{3d} + \text{CH}_3\text{OH}$. The calculated ΔH_{sp} (**3d**) is 9.2 kcal mol⁻¹. In acidic methanol solution, diprotonation is predicted not to proceed spontaneously.

Table 3 Calculated singlet transition energies (ΔE) and intensities (f) of monoprotinated eilatin molecule **2b** with C_s symmetry

Transition symmetry	Theoretical		Experimental ^a $\Delta E/\text{eV}$ (log ϵ)
	$\Delta E/\text{eV}$	f	
A'	2.76	0.756 ($\pi \rightarrow \pi^*$)	2.82 (4.33)
A'	3.20	0.094 ($\pi \rightarrow \pi^*$)	
A'	3.45	0.231 ($\pi \rightarrow \pi^*$)	
A''	3.67	0.000 ($n \rightarrow \pi^*$)	
A'	3.68	0.047 ($\pi \rightarrow \pi^*$)	
A'	3.92	0.099 ($\pi \rightarrow \pi^*$)	
A''	4.17	0.000 ($n \rightarrow \pi^*$)	
A''	4.28	0.000 ($n \rightarrow \pi^*$)	
A'	4.29	0.281 ($\pi \rightarrow \pi^*$)	
A'	4.32	0.062 ($\pi \rightarrow \pi^*$)	

^aRef. 1(b). ^bIn ref. 1(a), the value obtained is 4.60 eV.

The calculated electronic spectrum of **3d** is similar to that of **2b** and corresponds well to the electronic spectrum observed in acidic media. However, no pH-dependent study on the electronic spectrum of eilatin has been made. Therefore, we here limit ourselves to a mention of the possibility that **3d** exists in the acidic solution used in the study of Rudi and Kashman.¹

Triprotonation provides two isomers: 6,13,14- (**4a**) and 5,16,14-protonated (**4b**) eilatin molecules; Table 2 shows that **4a** is more stable.

This molecule has a twisted structure at the minimum, whereas the planar structure corresponds to the transition state. Since the zero-point energy of the flutter mode at the minimum (0.1 kcal mol⁻¹) is comparable to the energy difference between these structures (0.1 kcal mol⁻¹), **4a** most likely adopts the planar C_s structure (Fig. 3). The presence of two long C-C bonds (1.482 and 1.473 Å) suggests that **4a** (C_s) consists of 3-protonated and 3,6-diprotinated 3,6-DAZPH-like rings: the calculated ring charges are +1.22 and +1.78 e , respectively.

The heat of protonation [ΔH_{sp} (**4a**)] for the process, **3d** + $\text{CH}_3\text{H}_2\text{O}^+ \rightarrow \text{4a} + \text{CH}_3\text{OH}$, is calculated to be 99.3 kcal mol⁻¹. In acidic methanol solution, triprotonation does not spontaneously proceed.

The lowest transition energy of **4a** (C_s) is calculated to be 2.15 eV. This value is smaller than the lowest peak (2.82 eV) of the electronic spectrum observed in acidic media.

Tetraprotonated eilatin molecule **5** is calculated to have the twisted C_2 structure (Fig. 3) and the heat of formation is estimated to be 1178.4 kcal mol⁻¹. The heat of protonation for the process, **4a** + $\text{CH}_3\text{H}_2\text{O}^+ \rightarrow \text{5} + \text{CH}_3\text{OH}$, is calculated to be 167.8 kcal mol⁻¹. Tetraprotonation does not spontaneously proceed. The lowest transition energy is calculated to be 1.72 eV which is smaller than the lowest peak (2.82 eV) of the electronic spectrum observed in acidic media.

Techniques used: AM1 molecular orbital calculations

Tables: 6

Figures: 3

References: 10

Received, 29th April 1998; Accepted, 3rd June 1998
Paper E/8/03241F

References cited in this synopsis

- (a) A. Rudi, Y. Benayahu, I. Goldberg and Y. Kashman, *Tetrahedron Lett.*, 1988, **29**, 6655; (b) A. Rudi and Y. Kashman, *J. Org. Chem.*, 1989, **54**, 5331.
- (a) N. R. Shochet, A. Rudi, Y. Kashman, Y. Hod, M. R. El-Maghrabi and I. Spector, *J. Cell. Physiol.*, 1993, **157**, 481; (b) L. A. McDonald, G. S. Eldredge, L. R. Barrows and C. M. Ireland, *J. Med. Chem.*, 1994, **37**, 3819; (c) M. Lishner, I. Shur, I. Bleiberg, A. Rudi, Y. Kashman and I. Fabian, *Leukemia*, 1995, **9**, 1543; (d) M. Einat, M. Lishner, A. Amiel, A. Nagler, S. Yarkorli, A. Rudi, Y. Kashman, D. Markel and I. Fabian, *Exp. Hematol.*, 1995, **23**, 1439; (e) M. Einat, A. Nagler, A. Amiel, M. D. Fejgin, A. Rudi, Y. Kashman and I. Fabian, *Leukemia Res.*, 1996, **20**, 751.
- S. Nakahara, Y. Tanaka and A. Kubo, *Heterocycles*, 1993, **36**, 1139.
- G. Gellerman, M. Babad and Y. Kashman, *Tetrahedron Lett.*, 1993, **34**, 1827.
- A. Rudi, Y. Kashman, D. Gut, F. Lellouche and M. Kol, *Chem. Commun.*, 1997, 17.
- Mopac 93 release Fujitsu limited, 1994.
- M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
- H. Baumanns, *QCPE*, 1977, **11**, 333; G. Buemi, *QCMP*, #062; H. Kihara, JCPE Program No. 84, 1993.