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Synthesis and Spectroscopic Properties of 1*H*-Cyclohepta[2,1-*b*:3,4-*b'*]diindole and Molecular Structure of its Protonated Species

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Abstract The title compound **9** was synthesized by condensation of 2,2'-biindole and 1-chloro-3-(*N,N*-dimethylamino) propenium chloride in 1,2-dichloroethane. NMR and UV-vis absorption spectra of **9** under neutral, acidic and basic conditions were discussed in respect of its protonation and deprotonation. A crystal structure of its protonated species, **9H$^+$TfO$^-$**, was determined by X-ray diffraction analysis, indicating its planar and symmetrical structure. Change of absorption spectra of **9** in the presence of a large excess of various metal ions was studied to find out a mode of interaction between **9** and metal ion.

Keywords Biindole, Azaazulene, Azepine, X-ray structure, Absorption spectra, DFT calculations

1. Introduction

There were reported two marine natural products having two indole units around a fully unsaturated seven-membered ring, iheyamine A (**1**) [1] and cauresin (**2**) [2–5], the former of which exhibits cytotoxic activity against tumor cells. [1] In respect to their unique structures and biological activity, various compounds (**3**–**8**) structurally related to **1** and **2** have been synthesized (Figure 1). [3–6]

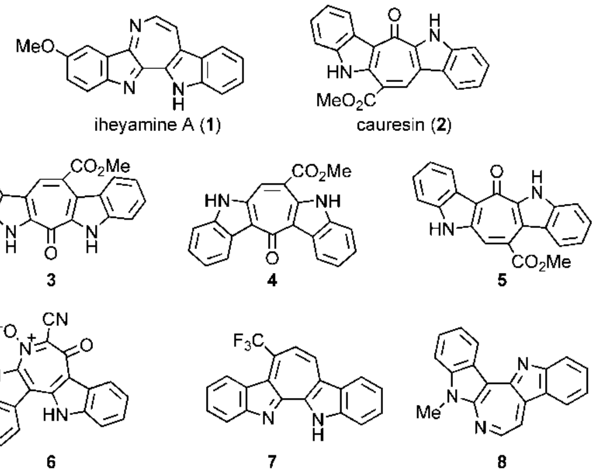


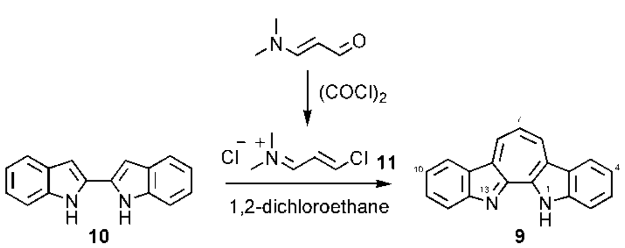
Figure 1. Marine natural products (**1**–**2**) having two indole units and structurally related synthetic compounds (**3**–**8**)

However, basic structural features and spectroscopic properties of a simple compound without any substituent for these π-conjugated systems have not been reported yet. Herein we describe synthesis of the title compound **9**, 1*H*-cyclohepta[2,1-*b*:3,4-*b'*]diindole, which is the parent compound for **7**, its absorption properties under various conditions, and also X-ray structure of its trifluoromethanesulfonic acid (TfOH) salt.

2. Results and Discussion

2.1. Synthesis and properties of 1*H*-cyclohepta-[2,1-*b*:3,4-*b'*]diindole (9)

The title compound **9** was synthesized, in a similar way of Baraznenok *et al.*, [6] by condensation of 2,2'-biindole (**10**) [9] with 1-chloro-3-(*N,N*-dimethylamino)propenium chloride (**11**), which was generated *in situ* by reaction of 3-dimethylaminoacrolein with oxalyl chloride (Scheme 1) [10].



Scheme 1. Synthesis of **9**

The compound **9** was isolated as dark red plates in 57 % yield. The structure of **9** was confirmed by spectroscopic

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analysis and the results of X-ray crystallographic diffraction of its protonated compound (*vide infra*). Seven signals in the ^{1}H-NMR spectrum of **9** and ten signals in the ^{13}C-NMR indicate its symmetrical structure around the central molecular axis through the 7 carbon atom, concomitantly evidencing a faster hydrogen shift between two tautomeric structures than the NMR time scale. It is worthy to note that there is a relatively large difference of proton chemical shifts between the 6(8) and 7 positions ($\Delta\delta = 1.20$ ppm), as seen in azulenes and azaazulenes, which have alternatively fluctuated π-electron density around their peripheral ring frameworks [11, 12].

The UV-vis spectrum of **9** in CH_3CN exhibits mainly two absorption bands, strong band around 330 nm and weak band at 495 nm (Figure 2). In an acidic medium of trifluoroacetic acid (TFA), the long wavelength absorption exhibits a blue shift by 35 nm and color of the solution turns to yellow orange. On the other hand, in a basic medium of 16% NaOH aq. in DMSO, both absorption bands show a red shift. While the shift value of the short wavelength absorption is small as 9 nm, that of the long wavelength absorption is 31 nm. Color of the basic solution is bright red, which is visibly distinguishable from those of the neutral (dark red) and acidic (yellow orange) solutions. The color changes under acidic and basic conditions can be attributed to the protonation and deprotonation of **9** to generate ionic species, **9H**$^+$ and **12** (Scheme 2), respectively. Formation of these ionic species was confirmed by ^{1}H NMR data in TFA-d_1 and NaOD/DMSO-d_6; [13] *i.e.,* the hydrogens of **9H**$^+$ (δ_{ave} 8.25 ppm) are deshielded and those of **12** (δ_{ave} 7.91 ppm) slightly shielded compared with that of **9** (δ_{ave} 7.93 ppm) in $CDCl_3$.

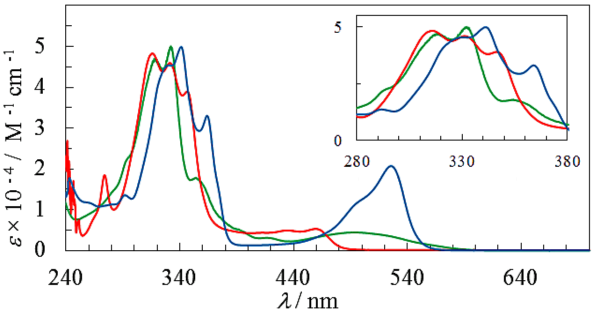
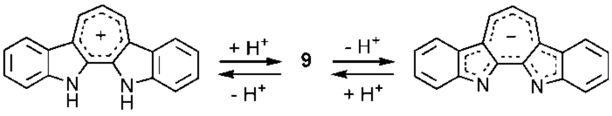


Figure 2. Absorption spectra of **9** in CH_3CN (green), TFA (red), and NaOH aq./DMSO (blue). Inset is expanded spectra at a range of 280–380 nm



9H$^+$ **12**

Scheme 2. Protonation and deprotonation of **9**

The crystal structure of a TfOH salt of **9** was determined by X-ray crystallographic analysis. There are two independent molecules of **9H**$^+$ with slightly different bond lengths and angles in a cell. ORTEP drawings of one of the structures are shown in Figure 3. The structure of **9H**$^+$ is planar and almost symmetrical around a central molecular axis through the C7 carbon atom. Average bond lengths of the two different molecules of **9H**$^+$ and its calculated structure at the B3LYP/6-31G(d) level of theory [14] are shown in Figure 4. Difference between them is less than 0.017 Å, indicating that the results of calculations at the level of theory are reliable. Since difference of bond lengths of the seven-membered ring in the calculated structure of **9H**$^+$ is less than 0.046 Å and average of their bond lengths is 1.410 Å, the ring indicates bond-convergency, besides the benzene rings. On the other hand, the calculated structure of **9** has maximum difference of bond lengths of the seven-membered ring is 0.087 Å, indicating slight bond-alternation around the seven-membered ring.

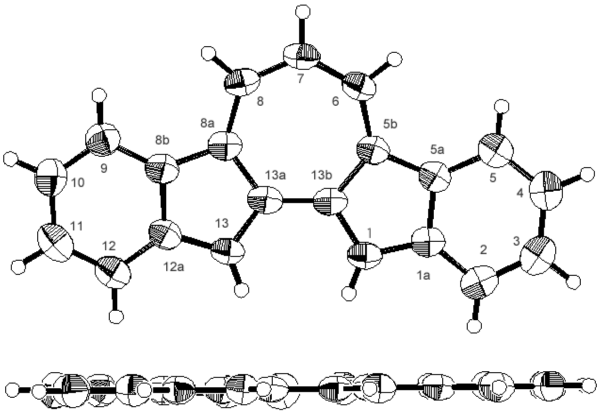


Figure 3. ORTEP drawings of **9H**$^+$**TfO**$^-$, one of two different molecules. Top views (top) and side view (bottom). The counter anion (TfO^-) was omitted

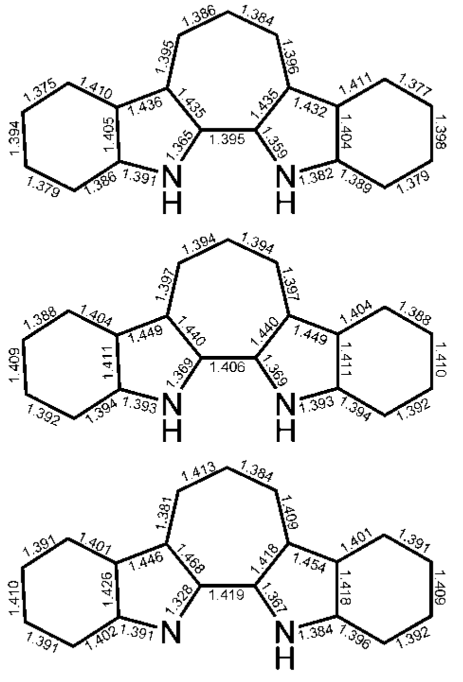


Figure 4. Average bond lengths (in Å) of the crystal structures of **9H**$^+$**TfO**$^-$ (top) and bond lengths of the calculated structures of **9H**$^+$ (middle) and **9** (bottom)

Changes of the absorption spectrum of **9** were also observed in the presence of metal ion. While any clear change was not observed in the presence of Li^+, Na^+, and Ag^+, the spectrum varied in the presence of other metal ions. The spectra of **9** in the presence of Mg^{2+}, Hg^{2+}, and Pb^{2+} are very similar to the one observed in TFA, suggesting that these metal ions probably interact with **9** like protonation to form complex A, shown in Figure 6. On the other hand, the spectra of **9** in the presence of Zn^{2+} and Cd^{2+} are different from these spectra, showing a slightly intense shoulder band at 360 nm and two relatively intense absorption bands at a range between 450–550 nm (Figure 5). For these metal ions, **9** may form bidentate complex B. According to Shannon [16], the order of ionic radii of these divalent metal ions is Pb^{2+} (0.98 Å) > Cd^{2+}(0.78 Å) > Hg^{2+}(0.69 Å) > Zn^{2+}(0.60 Å) > Mg^{2+}(0.57 Å). Therefore, Mg^{2+} seems to be too small and Pb^{2+} too large for their bidentate complexation with **9**. Although the ionic radius of Hg^{2+} is between Cd^{2+} and Zn^{2+}, nature of its softness [17] may make difficult to form a stable complex with **9**, which has relatively more electronegative nitrogen atoms as a ligand center. In order to clarify this hypothesis, isolation of the metal-ion complexes of **9** is now under progress.

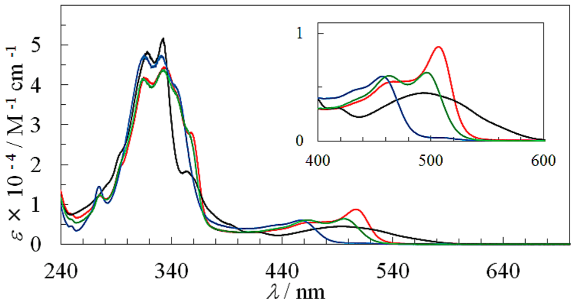


Figure 5. Absorption spectra of **9** in the presence of a large excess (100 eq.) of Li^+ (black), Mg^{2+} (blue), Zn^{2+} (green), and Cd^{2+} (red). Inset is expanded spectra at a range of 400–600 nm

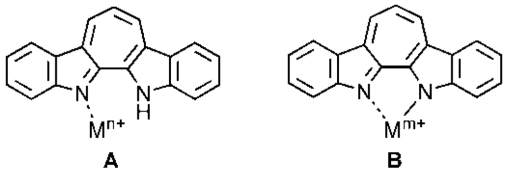


Figure 6. Modes of complexation of **9** with metal ions

3. Experiments

3.1. General

Melting points were measured on a Yanaco MP-3 and are uncorrected. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. UV-vis spectra were measured on a Shimadzu UV-2550 spectrometer. ^1H- and ^{13}C-NMR spectra were recorded on JEOL λ 400 and ECA500 spectrometers. Chemical shift value of tetramethylsilane (δ= 0 ppm) for ^1H-NMR and ^{13}C-NMR spectra was used as internal standard. Mass spectra were measured on a JMS-700 mass spectrometer. Column chromatography was performed with Silica gel 60N from Kanto Chem. Co. 1,2-Dichloroethane was purchased from Kanto Chem. Co. and was distilled over CaH_2. Oxalyl chloride was purchased from Wako Chem. Co. and was used without purification. TfOH and TFA were purchased from Tokyo Chem. Industry, Inc. 2,2'-Biindole was prepared in two steps from *o*-anisidine according to a procedure reported by Bergman *et al.* [9]

3.2. 1*H*-Cyclohepta[2,1-*b*;3,4-*b'*]diindole (9)

A solution of 119 mg (1.20 mmol) of *N*,*N*-dimethylamino-acrolein in 3 mL of 1,2-dichloroethane (DCE) was added to an ice-cooled solution of 151 mg (1.00 mmol) of oxalyl- chloride in 2 mL of DCE. To this mixture was added a suspension of 232 mg (1.00 mmol) of 2,2'-biindole (**10**) in 15 mL of DCE and the mixture was refluxed on an oil bath for 16 h under nitrogen atmosphere. The resulted bright yellow reaction mixture was poured into a saturated Na_2CO_3 aqueous solution and the water layer was extracted with chloroform (50 mL x 3). The combined organic layer was washed with a brine and was dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography eluted with 5%EtOH-chloroform to give 154 mg (57% yield) of **9** as dark red plates, m.p. = 297–298°C. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.72 (br. 1H, N–H), 7.46 (t, J = 7.7 Hz, 2H, H-4,10), 7.56 (t, J = 7.7 Hz, 2H, H-3,11), 7.64 (d, J = 7.7 Hz, 2H, H-2,12), 7.70 (t, J = 10.0 Hz, 1H, H-7), 8.36 (d, J = 7.7 Hz, 2H, H-5,9), 8.90 (d, J = 10.0 Hz, 2H, H-6,8) ppm; ^1H NMR (400 MHz, TFA-*d*) δ = 7.67 (t, J = 7.3 Hz, 2H, H-4,10), 7.87 (t, J = 7.3 Hz, 2H, H-3,11), 7.90 (d, J = 7.3 Hz, 2H, H-2,12), 8.29 (t, J = 9.9 Hz, 1H, H-7), 8.42 (d, J = 7.3 Hz, 2H, H-5,9), 9.32 (d, J = 9.9 Hz, 2H, H-6,8) ppm; ^1H NMR (400MHz, 16% NaOD- D_2O/DMSO-d_6 = 1 : 0.6) δ = 7.36 (t, J = 7.8 Hz, 2, H-4,10), 7.38 (t, J = 9.5 Hz, 1H, H-7), 7.58 (t, J = 7.8 Hz, 2H, H-3,11), 7.95 (d, J = 7.8 Hz, 2H, H-2,12), 8.33 (d, J = 7.8 Hz, 2H, H-5,9), 8.84 (d, J = 9.5 Hz, 2H, H-6,8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 115.4 (C-2,12), 120.3 (C-5,9), 122.1 (C-7), 122.4 (C-4,10), 126.3 (C-5a,8b), 129.3 (C-8,11), 131.1 (C-5b,8a), 132.4 (C-6,8), 142.0 (C-13a,13b), 144.5 (C-1a, 12a) ppm; IR (KBr) ν_{max} = 1402vs, 1393vs, 1215s, 1203s, 732s cm^{-1}; UV-vis (CH_3CN) λ_{max} = 318 (logε = 4.67), 332 (4.70), 353 (4.25), 394sh (3.69), 419 (3.45), 494 (3.65) nm; MS (70 eV) *m/z* (rel int.) = 268 (M^+, 100), 267 (13), 266 (11), 240 (4), 134 (10). HRMS Calcd for $C_{19}H_{12}N_2$ 268.1001; Found 268.1001.

3.3. 1,13*H*-Cyclohepta[2,1-*b*;3,4-*b'*]diindolium triflate ($9H^+TfO^-$)

To a solution of 11.2 mg (74.6 μmol) of TfOH in 10 mL of dichloromethane was added 20.0 mg (74.6 μmol) of **9**. The solvent was removed under reduced pressure and the residue was recrystallized from a mixture of dichloromethane and hexane to give 27.0 mg (88% yield) of $\mathbf{9H^+TfO^-}$ as yellow solids, m.p. > 300°C. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.51 (s, 2H, N–H), 7.60 (t, J = 7.9 Hz, 2H, H-4,10), 7.83 (t, J = 7.9

Hz, 2H, H-3,11), 8.05 (d, J = 7.9 Hz, 2H, H-2,12), 8.23 (t, J = 10.0 Hz, 1H, H-7), 8.38 (d, J = 7.9 Hz, 2H, H-5,9), 9.27 (d, J = 10.0 Hz, 2H, H-6,8) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 114.5, 120.7, 124.2, 124.7, 126.2, 131.7, 132.5, 135.1, 136.9, 141.2 ppm [15]; IR (KBr) $\nu_{\max}$ = 1620s, 1397vs, 1295vs, 1254s, 1210vs, 1166vs, 1027vs, 749vs, 731s, 635s cm^{-1}. A sample for X-Ray crystallographic analysis was obtained by further recrystallization from methanol.

3.4. X-Ray Crystallographic Analysis of $\mathbf{9H^+TfO^-}$

Diffraction measurements were conducted using a Rigaku R-AXIS RAPID diffractometer at –100 °C. Crystal data for $\mathbf{9H^+TfO^-}$ are as follows; triclinic, space group; P-1 (# 2), a; 7.0362(2) Å, b; 12.5278(3) Å, c; 20.7784(4) Å, α; 96.7827(7)°, β; 90.0115(7)°, γ; 90.0034(7)°, V; 1818.76(6) Å^3, Z; 4, R; 0.0893, $wR2$; 0.2353, $R1$; 0.0729 (I>2.00σ(I)), and S; 1.092. The relatively large R values are mainly attributed to thermal vibration of fluorine atoms of the triflate anion. Tables of fractional atomic coordinates, thermal parameters, bond lengths, and angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (CCDC 1038190) [Derect line: +44 1223 762910, Fax: +44 (0) 1233 336033, e-mail: deposit@ccdc.cam.ac.uk].

4. Conclusions

We have demonstrated that the title parent compound **9** could be synthesized from 2,2'-biindole (**10**) by its condensation with 1-(*N,N*-dimethylamino)-3-chloropropenium chloride. Compound **9** shows not only basic nature but also acidic nature. Spectral changes of UV-vis and NMR spectra were discussed based on protonation and deprotonation of **9**. Changes of the UV-vis spectrum in the presence of various metal ions were also described.

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