Identification of Sulfonic Phthalocyaninatozinc Isomers

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A combination of UV–vis, HPLC, and NMR methods was used to identify isomers of mono- and disulfonic phthalocyaninatozinc, which provides a good reference for isomer research of such compounds.

The application as sensitizer for photodynamic therapy (PDT) is one of the most interesting aspect of phthalocyanine (Pc) chemistry. Current reports[1,2] indicated that amphiphilic properties can be an advantage to photosensitizer performance. However, most amphiphilic Pcs are unequally substituted and may contain more or less constitutional isomers. For the sake of drug safety and efficiency, challenges are raised by isomer separation and structure identification. HPLC and NMR are commonly agreed to be powerful tools for these purposes. By now, many excellent results have been achieved for some equally substituted Pcs,[3–5] but only a few for unequally substituted compounds.[6,7] Recently, we obtained monosulfonic phthalocyaninatozinc (ZnPcS1 for short, Figure 1) and five isomers of disulfonic phthalocyaninatozinc (ZnPcS2 for short, Figure 2), respectively.[8,9] In this present paper we report the structure identification of them by combining NMR, HPLC, and UV–vis methods.

By optimizing the elution system, almost all isomers of sulfonic ZnPc could be distinguished on the present HPLC analysis (Figure 3). Quantitative analysis at 670 nm (Q-band) showed each group of isomers with the same substituent number had very close distribution to statistic proportion, except for those of ZnPcS2.[9,10] Online spectra of the five isomers of ZnPcS2 were obtained by photodiode array detector (PAD), which showed Q-band splits of 8 and 9 while normal Q-band absorption of 10, 11,

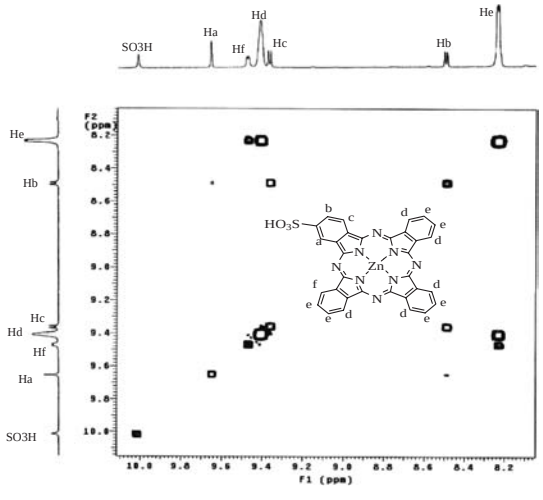

Figure 1. H–H COSY spectra of ZnPcS1 in DMSO-d_6. The inset is the structure and H label of ZnPcS1.

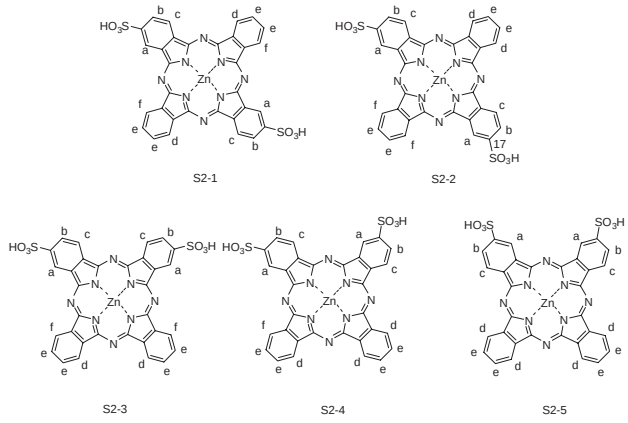

Figure 2. Structure and H label of ZnPcS2 isomers.

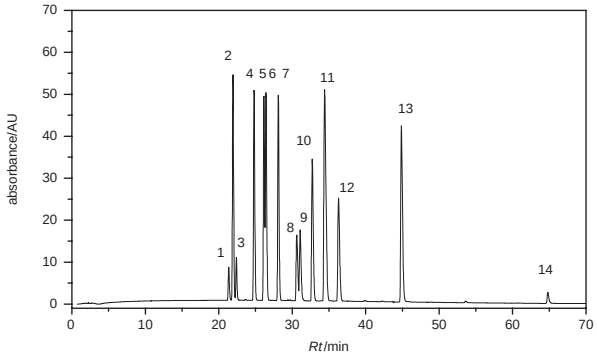

Figure 3. Analysis HPLC graph of mixture of sulfonic ZnPcs.[14] Peaks 1–3 are isomers of ZnPcS4. Peaks 4–7 are isomers of ZnPcS3. Peaks 8–12 are isomers of ZnPcS2. Peak 13 is ZnPcS1. Peak 14 is ZnPc.

and 12. This indicated that 8 and 9 are trans isomers (with structure as either S2-1 or S2-2 on Figure 2) and the others are cis isomers.[9–11] This result also agreed with that proposed by Ali et al.[12] When detected at 350 nm (B-band of phthalocyanine), ZnPcS2's isomer distribution (1.0:1.0:1.1:2.0:1.3) was very close to the statistic proportion (1:1:1:2:1). Then the highest peak 11 among them could be assigned to S2-4 (see Figure 2 for structure).[11] On the basis of these results we proposed that the elution order of ZnPcS2 isomers may depend on the relative distance of the sulfonic group on the phthalocyanine ring, i.e. the isomer with greater distance between the two sulfonic groups will be eluted earlier. So peak 8 to 12 were speculated to be S2-1 to S2-5 respectively in sequence. Further identification should depend on NMR.

As shown in Figure 1, ZnPcS1 has no structure isomer. Its ^{1}H NMR spectrum[13] (Figure 4) can provide very useful information to analyze the spectra of ZnPcS2 isomers. The ^{1}H signals of

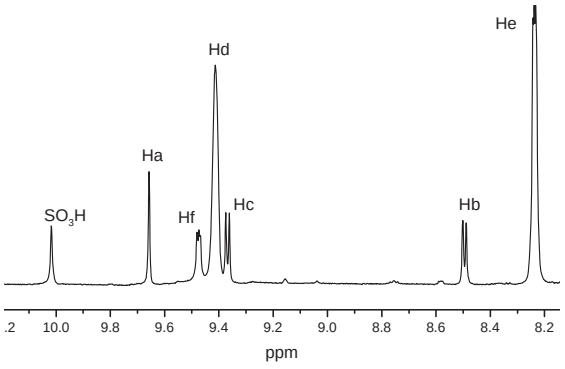

Figure 4. ^{1}H NMR spectra of ZnPcS1 in DMSO-d_6.

Table 1. Chemical shift (ppm) and assignment of ^{1}H of mono- and disulfonic phthalocyaninatozincs

HPLC Peak	13 (S1)	8 (S2-1)	9 (S2-2)	10 (S2-3)	11 (S2-4)	12 (S2-5)
He	8.24	8.25	8.26	8.26	8.25	8.26
Hb	8.50	8.49	8.49	8.49	8.48	8.50
Hc	9.37	9.38	9.38	9.36	9.37	9.37
Hd	9.41	9.44	9.45	9.44	9.43	9.44
Hf	9.48	9.48	9.50	9.49	9.49	—
Ha	9.66	9.64	9.65	9.64	9.65	9.65

ZnPcS1 were assigned (Table 1) based on coupling patterns and integrated intensities. A coupling of $J = 7.8$ Hz was assigned to the vicinal H_c (δ 9.37 ppm) and H_b (8.50 ppm). The singlet at 9.66 ppm was assigned to H_a, since it was the only proton without coupling. Thus, the influence of sulfonic substituent on the protons on the same subunit was clear. In short, the sulfonic substituent shifted the signals of protons on its ortho or para position to lower field, and those on meta position to higher field. This coincides with the fact that the sulfonic group reduces the electronic density of ortho and para positions, while increases that of the meta position of the substituted benzene ring. The two strongest signals were assigned unambiguously to protons of the unsubstituted isoindole subunits (δ 9.41 for H_d and δ 8.24 for H_e). On the basis of chemical shift and integral ratio, the multiplet at δ 9.48 was assigned to H_f. It indicates that the sulfonic substituent has a slight influence on its neighboring unsubstituted subunit and makes the signal of the nearest nonperipheral proton split from others. The finding of the H_f signal is a result of the instrument's high resolving power (600 MHz) and may greatly help the isomer identification of other sulfonic ZnPc. The above assignment was further confirmed by H–H COSY spectra (Figure 1), which showed cross-peaks of H_e–H_f, H_e–H_d, H_b–H_c, H_a–H_b, and H_d–H_f. The exchangeable signal at δ 10.00 was assigned to the sulfonic proton.

NMR data of ZnPcS2 isomers are presented in Table 1. Peak 11 of the HPLC now can be confirmed to be S2-4 for its unique triplet of H_b. Due to low symmetry S2-4 corresponds to the only structure that possesses unequal H_b among the ZnPcS2 isomers. Peak 12 was distinguished as S2-5 for the lack of H_f. As shown in Table 2, S2-5 is the only one that has no H_f. Then the remained cis isomer, 10 can be identified as S2-3. By now, the elution sequence of cis isomers was proven to coincide with the above-mentioned assumption that greatly separated of sulfonic group causes quick elution on HPLC.

Table 2. NMR characterization of sulfonic phthalocyaninatozincs for the identification of isomers

Phthalocyanine	S1	S2-1	S2-2	S2-3	S2-4	S2-5
Number of Hd	5	2	2	2	3	4
Number of Hf	1	2	2	2	1	0
Number of Hf-Hd coupling	1	2	0	2	1	0

In summary, we found the effect of sulfonic groups on NMR fingerprint characteristics of sulfonic ZnPc and the HPLC elution sequence of ZnPcS2. These findings will be helpful for isomer identification of similar compounds.

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References and Notes

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8 ZnPcS1 and the isomers of ZnPcS2 were isolated by one or two step/s of semi-preparative HPLC procedures from a phthalocyaninatozinc mixture which was synthesized by the mixed condensation of phthalonitrile, 4-sulfophthalonitrile and anhydrous zinc acetate in 2-methoxyethanol, with 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) as catalyst.
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12 All ^{1}H NMR spectra were recorded on a System-600, 600 MHz spectrometer (Varian) in DMSO-d_6, with nanoprobe as detector and tetramethylsilane (TMS) as standard.
13 Analytical condition: C18 column of 4.6 mm × 150 mm, particle size 5 μm (GraceSmart RP). Column temperature: 30 °C. A gradient condition was used with a flow rate of 1 mL·min^{-1}. Detection wavelength: 670 nm.
14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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