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The synthesis of water-soluble hemiporphyrazine analogues

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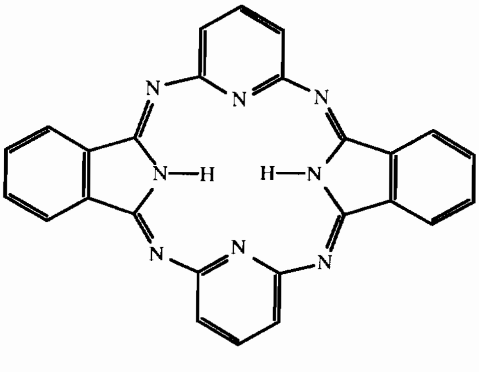
Abstract

The synthesis of a new class of water-soluble tetradentate macrocyclic complexes is reported. A hemiporphyrazine derivatized with pyridine groups about the periphery has been prepared. The copper(II) and nickel(II) complexes were synthesized from the free-base ligand. The peripheral pyridine groups of the free ligand and the metal complexes have been methylated to yield complexes exhibiting appreciable water solubility. Visible absorption spectra and cyclic voltammetric data are reported.

Introduction

The hemiporphyrazine ligand, H_2Hp, is a tetradentate macrocycle with nitrogen donor atoms first synthesized by Elvidge and Linstead [1]. As seen in Fig. 1, it shares many of the structural features exhibited by porphyrins and phthalocyanines—each is a N_4 macrocycle with an extended π system. Thus, the physical and chemical properties of H_2Hp and its metal complexes, M(Hp), are of obvious interest and a number of syntheses [1, 2], electrochemical studies [3], structural reports [4], and discussions of their electronic structures [5] have appeared in the literature.

A significant difference between H_2Hp and porphyrins or phthalocyanines is the lack of a four-fold rotation axis for this ligand. The structures of complexes of this ligand exhibit asymmetric M–N bond distances: the metal–pyridine nitrogen bond distances are longer than the metal–isoindole nitrogen bond distances by 0.08 Å in the four-coordinate Ni(II) complex which is considerably distorted from planarity [4], 0.21 Å in a six-coordinate Ni(II) complex [4c], and 0.25 Å in a six-coordinate Ge(IV) complex [4b]. What role this asymmetry plays in the physical and chemical properties of hemiporphyrazines is an area which has not been adequately explored due in part to the poor solubility these complexes exhibit. This is an area of interest in light of the rich photochemistry observed for porphyrins and phthalocyanines [6].



H_2Hp

Fig. 1. The hemiporphyrazine ligand, H_2Hp.

We wish to report the preparation and characterization of an analogue of the hemiporphyrazine ligand and its transition metal complexes with greatly enhanced solubility characteristics. Our efforts have focused on altering the periphery of the macrocycle by incorporating methylated pyridine groups to yield water-soluble analogues. The syntheses and characterization of the free-base macrocycles, H_2N_2Hp (**1**), and $H_2Me_2N_2Hp^{2+}$ (**2**), and transition metal complexes, $M(N_2Hp)$ (**3**) and $M(Me_2N_2Hp)^{2+}$ (**4**), (see Scheme 1) are reported herein.

Experimental

General information

Elemental analyses were performed by Desert Analytics, Tucson, AZ. IR spectra were recorded on a Perkin-Elmer 1600 Series FTIR. UV–Vis spectra were recorded on a Hewlett-Packard 8451A diode array spectrophotometer. For cyclic voltammetry measurements, an IBM EC/225 voltammetric analyzer was used in conjuction with a three-electrode cell supplied by

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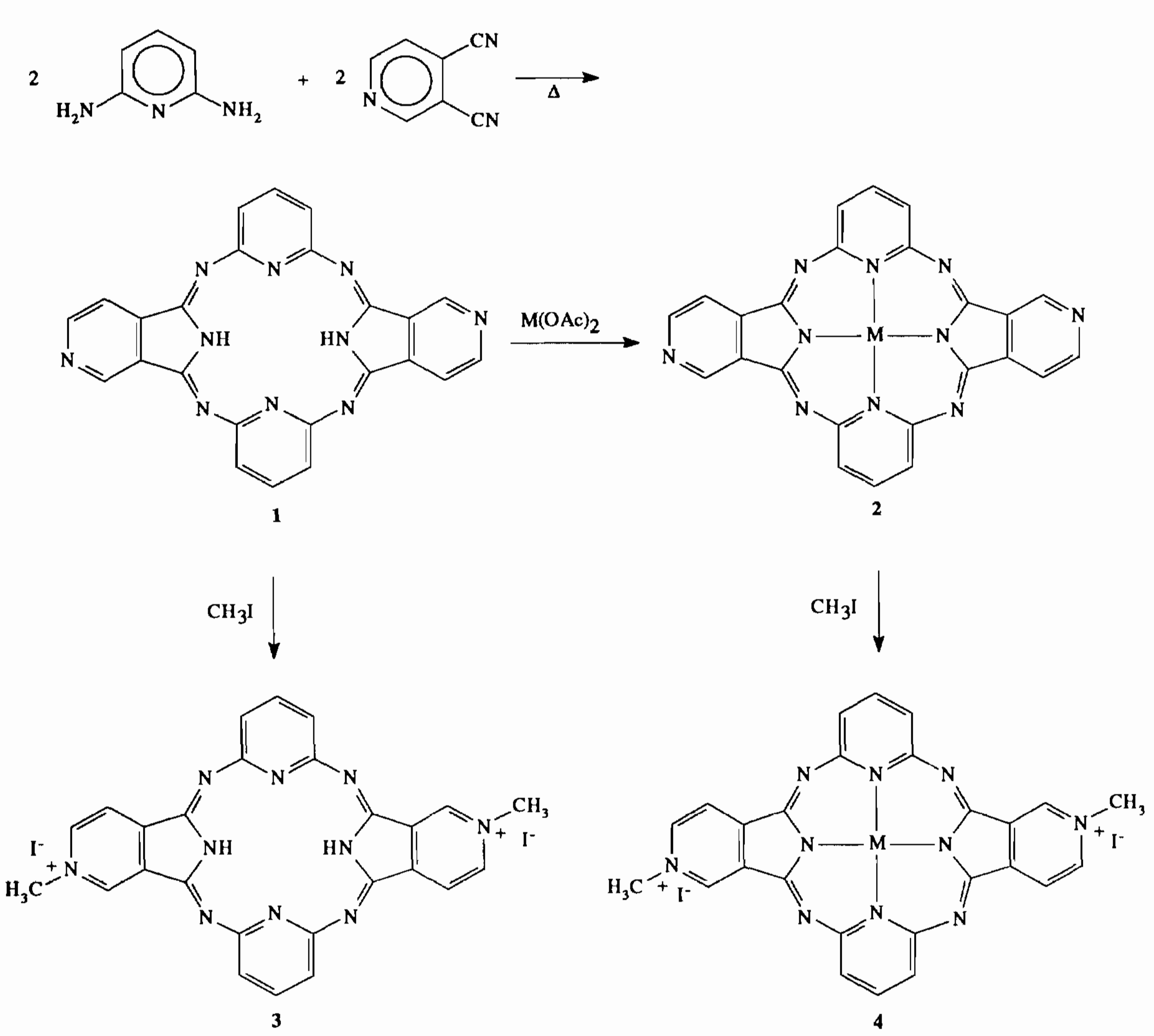

Scheme 1.

Bioanalytical Systems and composed of a Pt working electrode, Pt wire auxiliary electrode and an Ag/AgCl reference electrode. The dimethylformamide, DMF, or dimethyl sulfoxide, DMSO, solutions for voltammetric analyses were 10^{-3} M in electroactive species and 0.1 M in tetraethylammonium perchlorate. All samples were purged with nitrogen prior to examination. All solvents were spectral grade and used as received.

Synthesis of $H_2(N_2Hp)$

The macrocycle was synthesized in a manner analogous to that reported for H_2Hp [2a]. The preparation involves the condensation of 3,4-pyridinedicarbonitrile with 2,6-diaminopyridine in refluxing chloronaphthalene (see Scheme 1). In a typical preparation, 4.00 g (0.0310 mol) of 3,4-pyridinedicarbonitrile and 3.38 g (0.0310 mol) of 2,6-diaminopyridine were stirred in 25 ml chloronaphthalene at about 200 °C for 18 h. The product crystallized out as a red-brown powder (6.15 g, 90% yield). Depending on the relative orientation of the *exo* pyridine nitrogen atoms two isomers are likely, one with C_{2v} symmetry and the other with C_{2h} symmetry. However, no attempt was made to separate the isomers. Analytical samples were recrystallized from DMF. *Anal.* Calc. for $H_2Hp\cdot\frac{1}{2}H_2O$: C, 63.85; H, 3.35; N, 31.03. Found: C, 63.88; H, 3.24; N, 29.60%.

Synthesis of $H_2(Me_2N_2Hp)Cl_2$

The iodide salt of the methylated macrocycle was obtained by reaction of 1.01 g (2.26 mmol) of $H_2(N_2Hp)$ with 5.0 ml of methyliodide. The reaction was carried out in a stainless steel bomb employing a glass liner at 115–120 °C for 16 h. The crude product was recrystallized from 30 ml boiling water and washed with several 10 ml portions of cold absolute ethanol. A charcoal colored solid was obtained (0.84 g, 51% yield). The chloride salt was obtained by anion exchange chromatography on Dowex 1-X8 in the chloride form.

The eluent was evaporated to dryness and the residue was dried under vacuum at 150 °C for 6 h. *Anal.* Calc. for $[H_2Me_2N_2Hp]Cl_2 \cdot 2H_2O$: C, 53.89; H, 4.18; N, 24.17. Found: C, 53.99; H, 4.43; N, 23.49%.

Synthesis of $[Ni(Me_2N_2Hp)]Cl_2$

The macrocycle was metallated in a manner analogous to that reported for Ni(Hp) [1]. A boiling solution of 0.40 g of nickel(II) acetate in 20 ml of benzyl alcohol was added to a boiling solution of 0.60 g (1.36 mmol) of $H_2(N_2Hp)$ in 30 ml of nitrobenzene. After stirring for a few minutes, the solution was slowly cooled to room temperature. The nickel(II) derivative, $Ni(N_2Hp)$, crystallized as metallic green flakes (67% yield). The compound was methylated in a manner analogous to the free-base macrocycle (see above). A 0.125 g (0.250 mmol) sample was heated with 4.0 ml CH_3I in a glass-lined bomb at 120 °C for 22 h. 0.224 g of black, powdery solid was collected and washed with diethyl ether. A 120 mg sample was recrystallized from 20 ml boiling H_2O, collected by filtration and washed with ethanol. The sample was dried at 150 °C under vacuum. *Anal.* Calc. for $[Ni(Me_2N_2Hp)]I_2 \cdot H_2O$: C, 38.98; H, 2.52; N, 17.49. Found: C, 39.39; H, 2.53; N, 17.11%.

The chloride salt was isolated by anion exchange chromatography as described above for the free-base ligand. *Anal.* Calc. for $[Ni(Me_2N_2Hp)]Cl_2 \cdot 4H_2O$: C, 46.46; H, 3.90; N. 20.84. Found: C, 46.55; H, 3.64; N, 19.80%.

Synthesis of $[Cu(Me_2N_2Hp)]Cl_2$

A procedure analogous to that employed for $Ni(N_2Hp)$ was used to synthesize the copper(II) derivative. A yield of 47% was obtained. The iodide and chloride salts of the methylated derivative were isolated as for the Ni(II) complex. *Anal.* Calc. for $[Cu(Me_2N_2Hp)]Cl_2 \cdot 4H_2O$: C, 46.13; H, 3.87; N, 20.69. Found: C, 46.42; H, 2.93; N, 20.23%.

An analytical sample of the perchlorate salt of the copper(II) complex was isolated in an attempt to obtain a less hygroscopic analogue. **Caution**: Perchlorate salts of metal complexes with organic ligands are potentially explosive [7]. Although we have not observed detonation with this compound, care is urged. 50 mg of the chloride salt was stirred into a minimum amount of warm 85% ethanol. A total of about 1.5 ml of $NaClO_4$ saturated ethanol was added dropwise with stirring, whereupon a precipitate immediately formed. The slurry was cooled to room temperature and filtered. The solid was recrystallized from 18 ml boiling water with the addition of 1 ml saturated $NaClO_4$ in ethanol and washed well with cold ethanol and diethyl ether. 36 mg were collected. *Anal.* Calc. for $[Cu(Me_2N_2Hp)](ClO_4)_2$: C, 42.61; H, 2.48; N. 19.11. Found: C, 42.55; H, 2.30; N, 18.80%.

Discussion

The reaction sequences leading to the free-base and metalled macrocycle are represented in Scheme 1. Attempts to methylate the peripheral pyridine nitrogen with methyltosylate were unsuccessful. A very water-soluble, amorphous solid was invariably isolated, suggesting that the macrocycle decomposed. We are investigating the possibility that this decomposition is mediated by methylations occurring at the imino sites. As reported by Elvidge and Linstead [1], H_2Hp is not methylated by methyliodide, but is stable to the conditions used for attempted methylation. We were able to methylate both the free-base, H_2N_2Hp, and metallo derivatives with methyliodide. Successful reaction conditions required a large excess of methyliodide, a temperature of >110 °C, and an extended reaction time (overnight). The yields were essentially quantitative. The iodide salts, $[H_2Me_2N_2Hp]I_2$ and $[M(Me_2N_2Hp)]I_2$, are sparingly soluble in water and polar organic solvents.

Ion-exchange chromatography on Dowex 1X-8 in the chloride form was used to isolate the corresponding chloride salt of the free-base ligand, $[H_2Me_2N_2Hp]Cl_2$, and the metal complexes, $[M(Me_2N_2Hp)]Cl_2$, where M = Ni(II) or Cu(II). All of the chloride salts isolated tenaciously hold water, even after drying under vacuum at 150 °C. Elemental analyses of the chloride salts gave satisfactory results when waters of hydration were assumed to be present.

The $M(N_2Hp)$ complexes exhibit solubility in water under acidic conditions, but under these conditions macrocycle decomposition proceeds as evidenced by a gradual bleaching of the absorption bands. Acid hydrolysis of unsubstituted hemiporphyrazine complexes has been reported [1].

The spectra of H_2N_2Hp, $Cu(N_2Hp)$ and $Ni(N_2Hp)$ in DMSO are shown in Fig. 2 and are similar to those

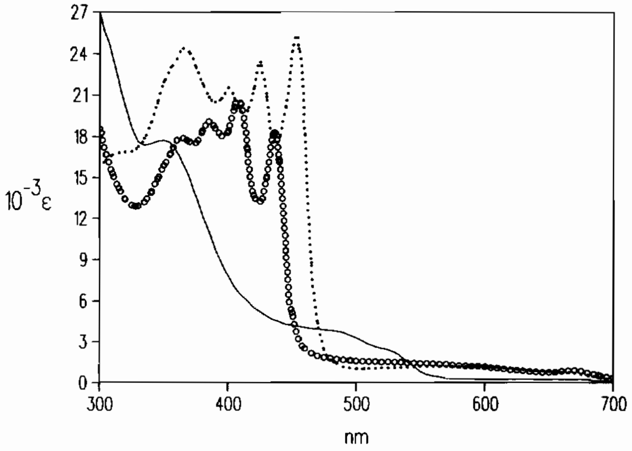

Fig. 2. Absorbance spectra of H_2N_2Hp, ——; $Cu(N_2Hp)$, ○○○○○○○; and $Ni(N_2Hp)$, · · · · · · ·, recorded in DMSO.

reported for the corresponding metallohemiporphyrazines in 50% vol./vol. DMSO/benzene [3]. These bands are assigned as ligand-centered $\pi \rightarrow \pi^*$ and/or $n \rightarrow \pi^*$ transitions based on molecular orbital calculations of the parent hemiporphyrazine ligand [5]. The similarities exhibited in the bands for the metallated species suggest that they are not charge-transfer in nature. The d–d bands for Cu(II) and Ni(II) hemiporphyrazines have been reported at wavelengths greater than 800 nm [4c]. The absorption spectra of $[H_2(Me_2N_2Hp)]Cl_2$, $[Ni(Me_2N_2Hp)]Cl_2$ and $[Cu(Me_2N_2Hp)]Cl_2$ in water are shown in Fig. 3. A comparison of Figs. 2 and 3 reveals a loss of structure in the blue region of the spectrum for the methyl pyridine analogues. We speculate that this may be a result of aggregation, similar to that observed for water-soluble phthalocyanines [8]. Perturbations in macrocycle π systems as a result of aggregation are known to result in spectral changes [9]. We are investigating this phenomenon. Interestingly, there is evidence of hemiporphyrazine stacking in the solid state: the structure of H_2Hp shows two aza nitrogens from other ligand molecules above and below the molecular plane at a distance of about 3.30 Å [10]. Porphyrin π–π dimers are well documented [11] as are porphyrin–phthalocyanine mixed aggregates [9].

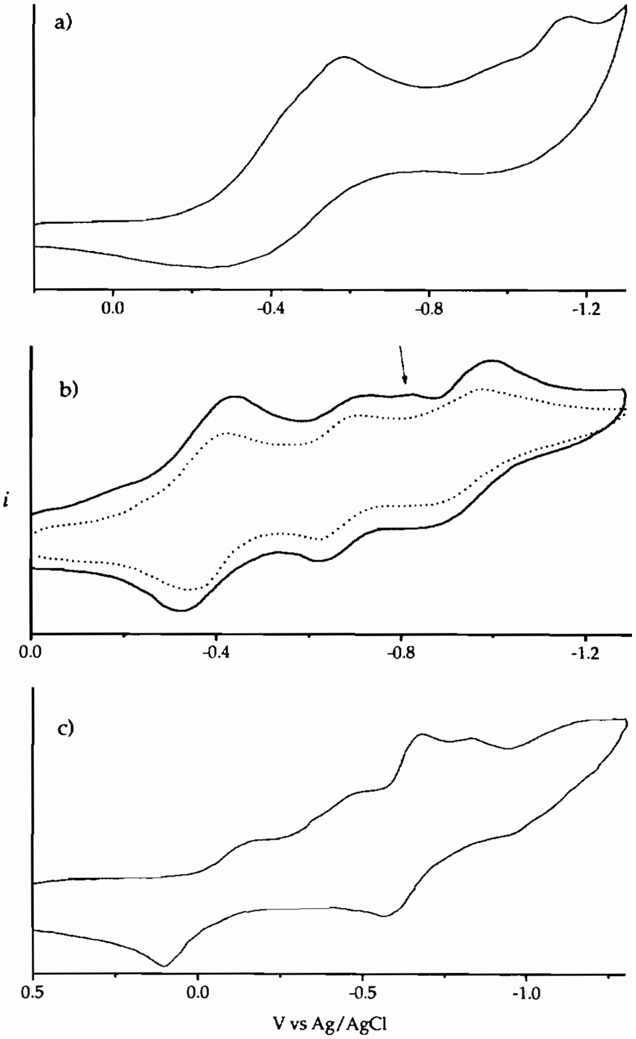

Fig. 4. Cyclic voltammograms for (a) $[H_2(Me_2N_2Hp)]I_2$ obtained at 20 mV/s; (b) $[Cu(Me_2N_2Hp)]Cl_2$ obtained at 20 mV/s; ·······, and 500 mV/s, ——; and (c) $[Ni(Me_2N_2Hp)]Cl_2$ obtained at 20 mV/s. All measurements were made in DMSO (0.1 M TEAP).

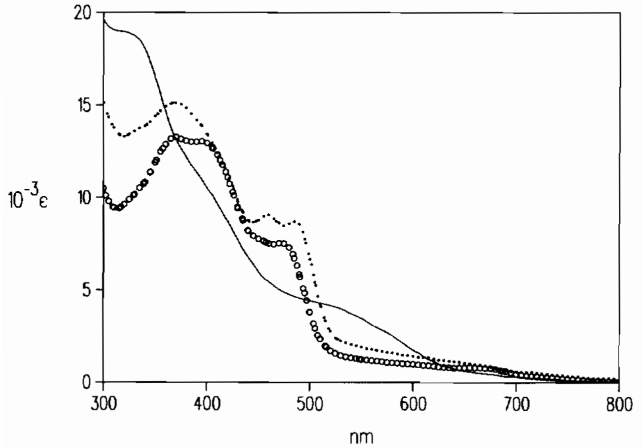

Fig. 3. Absorbance spectra of $[H_2(Me_2N_2Hp)]Cl_2$, ——; $[Cu(Me_2N_2Hp)]Cl_2$, ∘∘∘∘∘∘∘; and $[Ni(Me_2N_2Hp)]Cl_2$, ·······, recorded in H_2O.

The cyclic voltammograms of the free-base ligand and the metallated derivatives are shown in Fig. 4. Consistent with the presence of the positively charged substituents about the periphery of the ligand, reduction occurs at more positive potentials than have been observed for the corresponding unsubstituted hemiporphyrazines [3]. Scans in the positive direction up to the solvent limit revealed no oxidation steps. The free-base ligand exhibits two quasi-reversible waves. At slower scan rates, the Cu(II) analogue exhibits three reversible waves. Based on the electrochemical analysis of the parent hemiporphyrazine and its Cu(II) complex [3] and a comparison of the $[H_2(Me_2N_2Hp)]^{2+}$ cyclic voltammogram (Fig. 4(a)), the first reduction step for $[Cu(Me_2N_2Hp)]^{2+}$ involves a molecular orbital of primarily metal character and the remaining steps are ligand centered. As can be seen in Fig. 4, however, an additional reduction wave appears at −0.83 V versus Ag/AgCl at faster scan rates. Further studies are required to determine if this corresponds to an electronic reorganization. The electrochemical behavior of the Ni(II) analogue is complex. Two quasi-reversible waves are centered at −0.25 and −0.63 V versus Ag/AgCl. Additional reduction waves appear at −0.46 and −0.83 V versus Ag/AgCl. The relative heights of the reduction waves are scan rate independent from 20 to 200 mV/s.

Conclusions

Because of poor solubility characteristics, the reactivity patterns of hemiporphyrazine and metallo derivatives are not well established. A number of hemiporphyrazine analogues with markedly improved solubility characteristics have been synthesized. These new compounds may allow for photochemical and electrochemical studies which complement those of the structurally similar porphyrins and phthalocyanines. We are currently exploring the properties of these and similar species.

Acknowledgement

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