A Tautomerisable Macrocyclic Compound containing Two Aza-bridged 2,2'-Bipyridine Moieties

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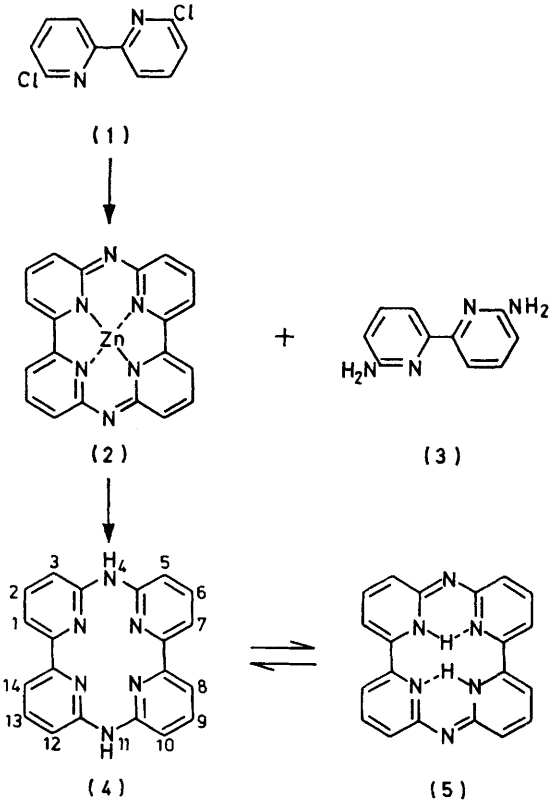
A novel macrocyclic compound containing two aza-bridged 2,2'-bipyridine moieties was prepared by the templated reaction of 6,6'-dichloro-2,2'-bipyridine. Spectroscopic investigation shows that the aza-bridging atoms form an amine ⇌ imine tautomeric system. The tautomerism is dependent upon the solvent; the imine form is preferred in non-polar solvents such as chloroform and benzene, while the amine form is favoured almost exclusively in polar solvents such as water, alcohol, acetonitrile, dimethyl sulphoxide, or tetrahydrofuran.

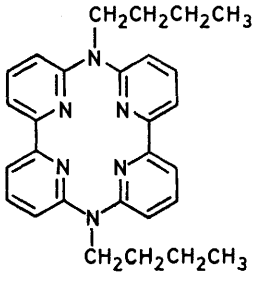
THE chemistry of synthetic aza-macrocycles and their metal complexes is in a stage of rapid development,[1] attempts having been made to relate their structural properties and reactivities with those of metalloporphyrins and corrins.

While prototropic tautomerisation of heteroaromatic amines to the corresponding imines has long been of interest,[2] little has been done to develop these compounds as macrocyclic agents. An interest in the tautomeric properties of diquinolylamines [3] has led us to synthesise a series of new macrocyclic compounds containing pyridine rings which may show potent tautomeric behaviour in various environments. We have recently reported the syntheses of conjugated macrocycles by thermal dimerisation of 1,10-phenanthroline derivatives,[4] and have studied the electronic structures of these compounds by means of *X*-ray photoelectron spectroscopy.[5] We report here the synthesis of a novel hexa-aza-macrocycle by the templated reaction of 6,6'-dihalogeno-2,2'-bipyridine and describe its unusual tautomeric properties.



The general scheme for the synthesis of the new ligand involves the template cyclisation of 6,6'-dichloro-2,2'-bipyridine with ammonium tetrachlorozincate, $(NH_4)_2ZnCl_4$, and subsequent demetallation of the resulting zinc complex.

6,6'-Dibromo-2,2'-bipyridine has previously been prepared by the inconvenient procedure of gas-phase bromination of 2,2'-bipyridine.[6] Hence we obtained 6,6'-dichloro-2,2'-bipyridine (1) by the reaction of 1,1'-dimethyl-2,2'-bipyridine-6,6'(1*H*,1'*H*)-dione [7] with PCl_5 in $POCl_3$. Fusion of 1 equiv. of (1) with 7 equiv. of $(NH_4)_2ZnCl_4$, which was obtained by heating $ZnCl_2$ and NH_4Cl in water,[8] afforded the zinc complex (2), m.p. 470 °C (decomp.) in 68% yield. Direct evidence for a metal-bound macrocycle is provided by the mass spectrum. The largest *m/e* values (400, 402, and 404) correspond to the complex of ^{64}Zn, ^{66}Zn, and ^{68}Zn, respectively, with abundance ratios consistent with the isotopic abundance of zinc. 6,6'-Diamino-2,2'-bipyridine (3) was also formed in 6% yield.



The zinc complex is quite stable in mineral acids, even in hot trifluoroacetic acid. Bubbling of dry hydrogen chloride through its solution in sulphuric acid barely gave the metal-free macrocycle (4) (50%, m.p. 460 °C decomp.). The molecular weight of (4) was confirmed by the high-resolution mass spectrum. The i.r. spectrum exhibited no absorption in the normal N–H

stretching region, but a broad absorption at 2 800—3 000 cm^{-1} indicated the formation of an intramolecular N–H · · · N interaction, and thus supported the structure (5) rather than (4). In solution, however, it shows remarkable colour change with the solvent used. A solution in a non-polar solvent such as chloroform and benzene is deep yellow in colour, while that in water, alcohol, acetonitrile, dimethyl sulphoxide, or other polar solvents is almost colourless. In chloroform, the fully conjugated imine form is thought to predominate, and leads to absorption of light in the visible region, whereas in acetonitrile or other polar solvents the partially conjugated amine form is the major form. As a model compound of (4), di-n-butyl macrocycle (6) was prepared from (4) by treatment with sodium hydride and then with n-butyl iodide in dioxan. The ^1H n.m.r. spectrum shows that the two n-butyl groups are situated on nitrogen bridges as in (6), because the protons of the pyridine rings give rise to only three signals. The spectrum of this compound shows only small solvent dependence.

The electronic spectra of the macrocycle and model compounds are shown in Figure 1. The spectrum of the

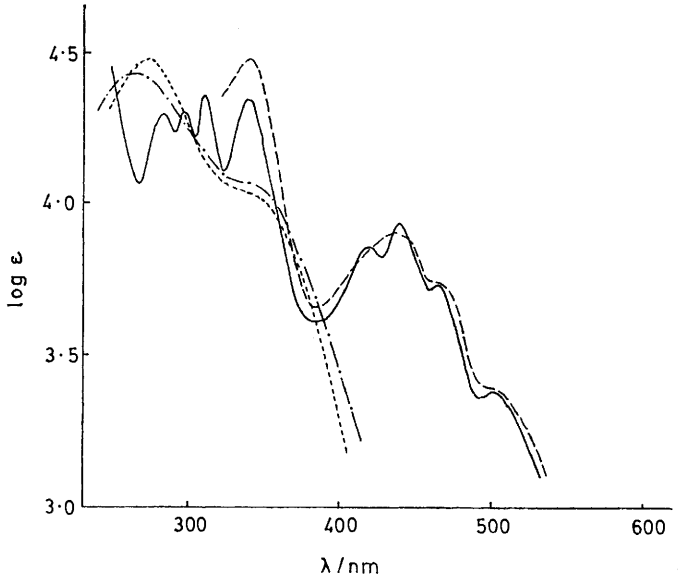


FIGURE 1 Electronic spectra of the hexa-aza-macrocycle in $CHCl_3$ (———) and in MeCN (— · — · —), the zinc hexa-aza-macrocycle in dimethyl sulphoxide (— — — —), and the di-n-butyl hexa-aza-macrocycle in $CHCl_3$ (– – – –)

macrocycle in acetonitrile is very similar to that of the dibutyl macrocycle (6), whereas the spectrum in chloroform is similar to that of the zinc complex (2) whose electronic structure may resemble that of (5). This fact indicates that the equilibrium is shifted in favour of the amine tautomer (4) in acetonitrile, whereas the imine form (5) is favoured almost exclusively in chloroform. The change in the structure with solvent may be described in terms of inter- and intra-molecular hydrogen bonding. Thus, as solvent polarity is varied in a mixture of solvents, the absorption moves continuously with clean isosbestic points. Typical spectra are shown

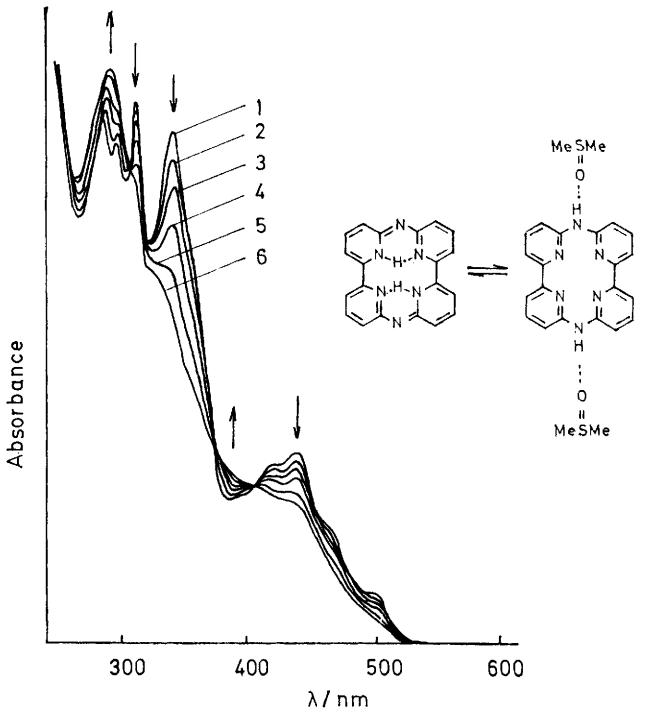


FIGURE 2 Spectral change of the macrocycle by addition of dimethyl sulphoxide in $CHCl_3$; [Macrocycle] = 2.80 × 10^{-5} mol l^{-1}, [DMSO] = 0 (1), 0.07 (2), 0.17 (3), 0.34 (4), 0.67 (5), and 0.98 (6) mol l^{-1} in $CHCl_3$. Arrows indicate the direction of the absorbance changes for increasing DMSO concentration

in Figure 2, which refers to measurements in chloroform–dimethyl sulphoxide. Isosbestic points were observed at 310 and 405 nm. Figure 3 shows relative absorbances at 340 nm in various solvent systems. It is interesting

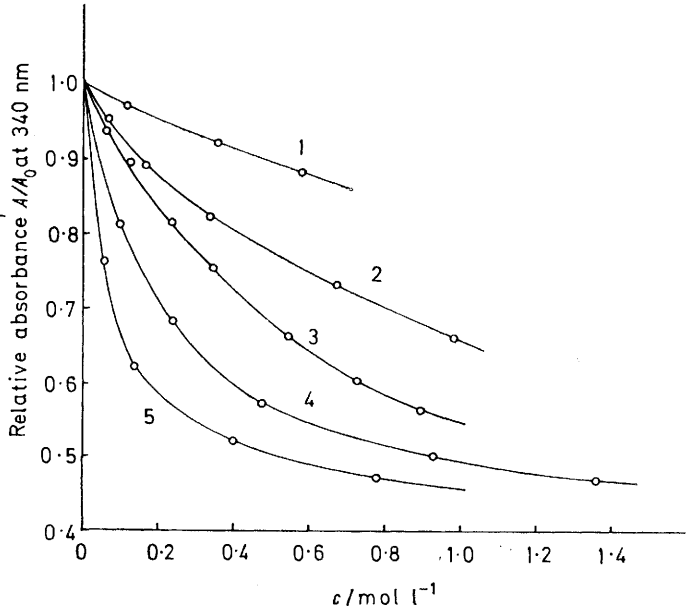
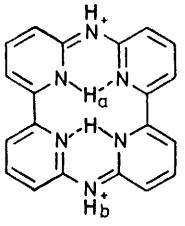


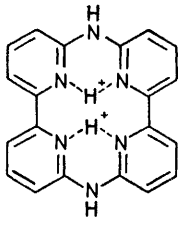
FIGURE 3 Variation of relative absorbance caused by addition of polar solvent to solutions of the hexa-aza-macrocycle dissolved in chloroform (2.80 × 10^{-5} mol l^{-1}), with A_0 being absorbance at zero-added polar solvent. Curve 1, ether; curve 2, dimethyl sulphoxide; curve 3, acetonitrile; curve 4, tetrahydrofuran; curve 5, methyl ethyl ketone

to note that di-(2-pyridyl)amine exists exclusively in the amine form,[9] and that the macrocycle prepared by dimerisation of 2,9-diamino-1,10-phenanthroline contains two hydrogen atoms within the macrocycle.[4]

The ^1H n.m.r. spectrum of (4) could not be determined in a neutral organic solvent owing to its limited solubility, but the spectrum in trifluoroacetic acid was obtained and showed two separate signals due to hydrogen atoms attached to the two kind of nitrogen atom; one is due to the inner NH protons which is abnormally deshielded (δ 17.2) and the other (at δ 10.2) is due to the outer NH protons. This indicated that the compound is present as a dication (7a) or (7b) in the solution. A paramagnetic ring current owing to a 4π-electron system of the macrocycle as well as the very strong hydrogen bonding within the ring seems to be the reason for the abnormal deshielding of the inner NH protons.



(7a)



(7b)

EXPERIMENTAL

I.r. spectra were measured for KBr discs with a JASCO IRA-1 spectrophotometer. N.m.r. spectra were determined with Hitachi R-20A (60 MHz) and R-22 (90 MHz) instruments with tetramethylsilane as internal reference. Mass spectra were obtained by direct insertion into the ion source of a Hitachi RMU-7M instrument. Electronic spectra were measured with a JASCO UVIDEC-505 spectrophotometer at 25 °C.

1,1′-Dimethyl-2,2′-bipyridine-6,6′(1H,1′H)-dione.—A mixture of 2,2′-bipyridine (20 g) and dimethyl sulphate (70 ml) was maintained at 100 °C for 1 h. After cooling, dry ether (200 ml) was added to the reaction mass with stirring. The hygroscopic white precipitate was used without further purification. To an ice-cooled solution of potassium ferricyanide (120 g) in water (400 ml) were added alternately in small portions a solution of sodium hydroxide (150 g) in water (500 ml) and a solution of the foregoing white solid in water (500 ml), whilst maintaining the temperature under 5 °C. The mixture was then adjusted to pH 8—9 by dropwise addition of concentrated hydrochloric acid solution with cooling and extracted with chloroform. After drying (Na_2SO_4), the solvent was evaporated off to afford a white solid which was recrystallised from benzene to give the diketone (18 g, 65%), m.p. 210—211 °C, $\nu_{max.}$ (KBr) 1 650 cm^{-1} (C=O); δ($CDCl_3$) 3.29 (6 H, s, NCH_3), 6.19 (2 H, dd, *J* 6.6 and 1.2 Hz), 6.67 (2 H, dd, *J* 9.0 and 1.2 Hz), and 7.39 (2 H, dd, *J* 9.0 and 6.6 Hz).

6,6′-Dichloro-2,2′-bipyridine (1).—The diketone (7.0 g), phosphorus pentachloride (15 g), and phosphoryl chloride (140 ml) were refluxed for 20 h. After removal of the excess of phosphoryl chloride by distillation under reduced pressure, ice–water was added and the solution basified with ammonia. The precipitate crystallised from benzene as *needles* (7.2 g, 99%), m.p. 218—219 °C (Found: C, 53.5; H, 2.8; N, 12.4. $C_{10}H_6Cl_2N_2$ requires C, 53.4; H, 2.7; N, 12.4%); δ($CDCl_3$) 7.28 (d, 5-H), 7.70 (t, 4-H), and 8.29 (d, 3-H).

Zinc Hexa-aza-macrocycle (2).—The dichloride (1) (2.0 g) and ammonium tetrachlorozincate (15 g) were mixed thoroughly in a mortar and heated under nitrogen at 320—330 °C for 6 h. Removal of the sublimed unchanged starting material (0.43 g, 22%), washing with water, treatment with 10% sodium hydroxide (100 ml), and further washing with water afforded a greenish yellow solid (1.8 g). The solid was heated in a sublimation apparatus at 200 °C and 0.5 mmHg for 3 h to give 6,6′-diamino-2,2′-bipyridine (3) as a sublimate (100 mg, 6%), m.p. 186 °C (lit.,[6] 185 °C). The residue was redissolved in aqueous 5% acetic acid and was reprecipitated with sodium hydroxide to give the *zinc hexa-aza-macrocycle* (2) (1.2 g, 68%), which crystallised from a small amount of acetic acid as fine yellow needles, m.p. 470 °C (decomp.) (Found: C, 59.8; H, 3.5; N, 20.5. $C_{20}H_{12}N_6Zn$ requires C, 59.8; H, 3.0; N, 20.5%); *m/e* 400, 402, and 404.

3,10-Dihydrotetrapyrido[2,1,6-de:2′,1′,6′-gh:2″,1″,6″-kl:2‴,1‴,6‴-na][1,3,5,8,10,12]*hexa-azacyclotetradecine* (4).—A stream of dry hydrogen chloride was passed through a solution of the zinc hexa-aza-macrocycle (2) (760 mg) in concentrated H_2SO_4 (30 ml) for 6 h, after which it was filtered on to ice and basified with aqueous ammonia. The precipitate was washed with dilute aqueous ammonia, and extracted with water. Recrystallisation from water afforded orange *needles* (320 mg, 50%), m.p. 460 °C (decomp.) (Found: C, 71.2; H, 3.9; N, 25.0%; M^+, 338.128 0. $C_{20}H_{14}N_6$ requires C, 71.0; H, 4.2; N, 24.8%. $^{12}C_{20}{}^1H_{14}{}^{14}N_6$ requires 338.128 0); δ[dication (7) in trifluoroacetic acid] 7.6 (d, 3-H), 8.2 (d, 1-H), 8.4 (t, 2-H), 10.2 (s, b-H), and 17.2 (s, a-H).

3,10-Di-n-butyl-3,10-dihydrotetrapyrido[2,1,6-de:2′,1′,6′-gh:2″,1″,6″-kl:2‴,1‴,6‴-na][1,3,5,8,10,12]*hexa-aza-cyclotetradecine* (6).—The *hexa-aza-macrocycle* (4) (40 mg) and sodium hydride (200 mg) were stirred in dioxan (10 ml) for 15 h at 20 °C. n-Butyl iodide (2 ml) was added to the mixture and was heated under reflux for 6 h, and allowed to cool. The excess of sodium hydride was destroyed by dropwise addition of methanol (2 ml) and the mixture was filtered. The filtrate was evaporated to dryness and the residue was washed with water. The yellow solid was chromatographed on alumina whence chloroform eluted a yellow band. The product crystallised from methanol as pale yellow *needles* (22 mg, 41%), m.p. 229—231 °C (Found: C, 75.0; H, 6.7; N, 18.3. $C_{28}H_{30}N_6$ requires C, 74.6; H, 6.7; N, 18.7%); *m/e* 450.254 8 (M^+) ($^{12}C_{28}{}^1H_{30}{}^{14}N_6$) requires 450.253 1); δ($CDCl_3$) 0.98 (t, CH_3), 1.49 (m, $NCH_2CH_2CH_2CH_3$), 1.82 (m, $NCH_2CH_2CH_2CH_3$), 3.99 (t, $NCH_2CH_2CH_2CH_3$), 6.89 (d, 3-H), 7.16 (d, 1-H), and 7.64 (t, 2-H).

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