Non-template Syntheses and Monoalkylation of an Aza Macrocycle containing 2,2'-Bipyridine

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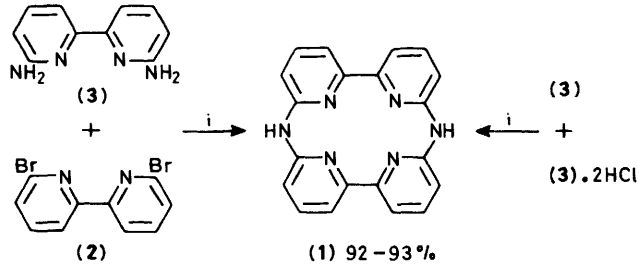
Cross-condensation of 6,6'-diamino-2,2'-bipyridine (**3**) with 6,6'-dibromo-2,2'-bipyridine (**2**) gave an azamacrocycle containing two aza-bridged 2,2'-bipyridine moieties, 3*H*,10*H*-tetrapyrido[2,1,6-*de*:2',1',6'-*gh*:2'',1'',6''-*kl*:2''',1''',6'''-*na*][1,3,5,8,10,12]hexa-azacyclotetradecine (**1**), in high yield without metal template. Furthermore, compound (**1**) could be obtained in >90% yield directly from 6,6'-dibromo-2,2'-bipyridine (**2**) by heating the latter with ammonia in an autoclave without metal template. *N*-Alkylation of compound (**1**) with n-hexyl bromide in the presence of tetra-n-butylammonium bromide gave exclusively the mono-*N*-n-hexyl derivative of (**1**), 10-hexyl-3*H*,10*H*-tetrapyrido[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**). Evidence for the tautomerism of the mono-n-hexyl derivative (**4**) was provided by the ^{1}H n.m.r. and absorption spectra.

Synthetic aza macrocycles and their metal complexes have been extensively studied because they have analogous structures to porphyrins and corrins;[1] however, little work has been carried out on their prototropic tautomerism, although the tautomerisation of heteroaromatic amines to the corresponding imines has long been the subject of investigation.[2] We have previously reported the synthesis of a tautomerisable macrocyclic compound (**1**) with unusual tautomeric properties, containing two aza-bridged 2,2'-bipyridine moieties by a zinc-template dimerisation, and also of its dialkyl derivative.[3]

We report here a simpler, more efficient synthesis of the aza macrocyclic compound (**1**) without metal template and also its selective mono-*N*-alkylation. The colour of solutions of the mono-*N*-n-hexyl derivative (**4**) was found to be dependent on the nature of the solvent; this was shown to be due to the tautomerism of (**4**), by the ^{1}H n.m.r. and absorption spectra.

Results and Discussion

Improved Synthesis of the Macrocyclic Compound (**1**).—6,6'-Dibromo-2,2'-bipyridine (**2**) was obtained by copper-induced dimerisation of 2-bromo-6-lithiopyridine according to the method of Parks *et al.*[4] 6,6'-Diamino-2,2'-bipyridine (**3**) was obtained as a by-product from the reaction of compound (**2**) with ammonium tetrachlorozincate,[3] or with a large excess of ammonia in an autoclave.[5] Although no reaction occurred when the diamine (**3**) was heated alone at 220—230 °C in a sealed ampoule, it was found to react with an equimolar amount of its dihydrochloride on being heated for 8 h at 220—230 °C in a sealed ampoule to give the macrocycle (**1**) in 93% yield. It also reacted with compound (**2**) in a similar manner to afford the macrocycle (**1**) in similar yield (Scheme 1).



Scheme 1. *Conditions:* i, 220 °C

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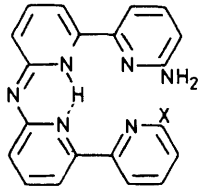
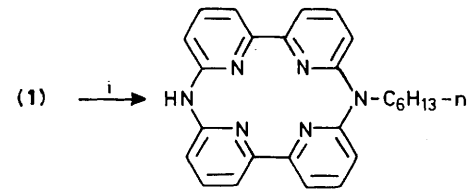
Polycondensation products were not obtained in either case. Although the pyridine rings of 2,2'-bipyridines rotate freely around the 2,2'-bond, such compounds readily undergo condensation to give a cyclic compound rather than linear polycondensation products. We reported previously the non-template self-condensation of 2,9-diamino-1,10-phenanthroline and its cross-condensation with 2,9-dichloro-1,10-phenanthroline.[6,7] Neither of these reactions gave polycondensation products, and it was suggested that the reaction intermediate must have a favourable configuration for dimerisation by formation of an intramolecular NH···N bridge [structure (**A**)]. In the cross-condensation of compound (**3**) with (**2**), it seems reasonable that a similar intermediate structure occurs, suppressing the polycondensation.



(**A**) X = NH_3Br, Br

Using the more efficient and convenient one-pot synthesis, the macrocycle (**1**) could be obtained when compound (**2**) was heated with ammonia gas under the appropriate pressure (Scheme 3). When the reaction pressure of ammonia was raised to 100 kg cm^{-2}, compound (**3**) was obtained instead of (**1**),[5] and the reaction was therefore carried out at 220—230 °C for 8 h under ammonia at 20 kg cm^{-2}; the essentially pure macrocycle (**1**) was thus obtained in 90% yield. Cross-condensation of compound (**3**) with its dihydrochloride or with (**2**) readily gives the macrocycle (**1**); a reasonable first step would therefore be the amination of (**2**) to give (**3**), which subsequently reacts with (**2**). It was confirmed that the macrocycle (**1**) does not decompose to give compound (**3**), even when heated with a large excess of ammonia under the conditions of the synthesis of (**3**) from compound (**2**). Thus, the amount or pressure of ammonia seems to affect the reaction of compound (**2**), determining the product (**1**) or (**3**), but does not affect the ammonolysis of the macrocycle (**1**). This improved procedure is not only simpler, but also gives the product (**1**) in a better yield (90%) than the two-step procedure involving a zinc-template reaction previously reported.[3]



Scheme 2. *Reagents:* i, NaOH, n-$C_6H_{13}Br$, Bu^n_4NBr, dioxane

*Selective Mono-*N*-alkylation of the Macrocyclo* (**1**) *and the Tautomeric Properties of the Mono-*N*-alkyl Macrocycle* (**4**).—In order to confirm the tautomerism of the macrocyclic compound (**1**), a tautomerisable and soluble derivative of (**1**) was synthesised. The mono-n-hexyl macrocyclic compound (**4**) was obtained from the reaction of compound (**1**) with n-hexyl bromide in dioxane using tetra-n-butylammonium bromide as a phase-transfer catalyst and sodium hydroxide (Scheme 2). The orange-yellow suspension of compound (**1**) and tetra-n-butylammonium bromide in dioxane became red on addition of sodium hydroxide. Subsequent addition of a large excess of n-hexyl bromide to the reaction mixture caused the precipitation of sodium bromide as the reaction proceeded. After purification, the mono-n-hexyl macrocycle (**4**) was obtained, in 75% yield, as the exclusive product in spite of the presence of a large excess of n-hexyl bromide; when sodium hydride was used as the base, the dialkyl derivative was obtained.[3] The change of colour observed in the reaction seems to be due to the formation of the anion of the macrocycle (**1**). The colour of the suspension could be quenched by the addition of water or methanol, thus suggesting that the use of tetra-n-butylammonium bromide as a phase-transfer catalyst gives the mono-anion of the macrocyclic compound exclusively.

The solution of compound (**4**) in chloroform was orange-yellow, changing to pale yellow on addition of methanol. The solid recovered from the chloroform solution of (**4**) was orange, and that from the methanol solution was pale yellow, although on redissolution in methanol both gave the same ^1H n.m.r. spectra. The absorption spectra of the mono-*N*-n-hexyl macrocycle (**4**) in chloroform and in methanol differ as shown in the Figure, while those of the dialkyl analogue are the same for both solvents. The spectrum of compound (**4**) in methanol was similar to those of the dialkyl macrocycle and of compound (**1**) in the same solvent.[3] ^1H N.m.r. measurements confirmed that the dependence of the colour of (**4**) in solution or as recovered solid on the solvent is due to prototropy. The aromatic signals of the monoalkyl derivative (**4**) in [$^2H_4$]-methanol showed a similar pattern to those of the dialkyl macrocycle [δ 7.16 (3 H), 7.64 (4 H), and 6.89 (5 H)] with small changes in chemical shift.[3] Thus the mono-n-hexyl macrocycle (**4**) in methanol must have the same conformation as the dialkyl macrocycle, and therefore the NH proton is out of the macrocyclic ring in methanol. This is consistent with the absorption spectra. On the other hand, the aromatic signals of compound (**4**) in [^2H]chloroform showed a different pattern from the dialkyl macrocycle. Moreover, a signal was observed at extremely low magnetic field (δ 16.7) which disappeared on shaking with D_2O; this therefore seems to be due to NH, and its extremely large chemical shift indicates that the NH proton of (**4**) in chloroform solution is within the macrocyclic ring. Thus the NH proton of (**4**) can be inside or outside the macrocyclic ring, depending on the nature of the solvent (Scheme 3).

This comprises a simpler and more efficient synthesis of the macrocyclic compound (**1**), which can then be further modified. It is difficult to elucidate the tautomeric properties of compound (**1**) using ^1H n.m.r. spectroscopy because of its very limited solubility in organic solvents. Although the dialkyl macrocycle, which is soluble in organic solvents, does not show tautomerism, the novel mono-n-hexyl derivative (**4**) has a different tautomeric structure in methanol or chloroform solution.

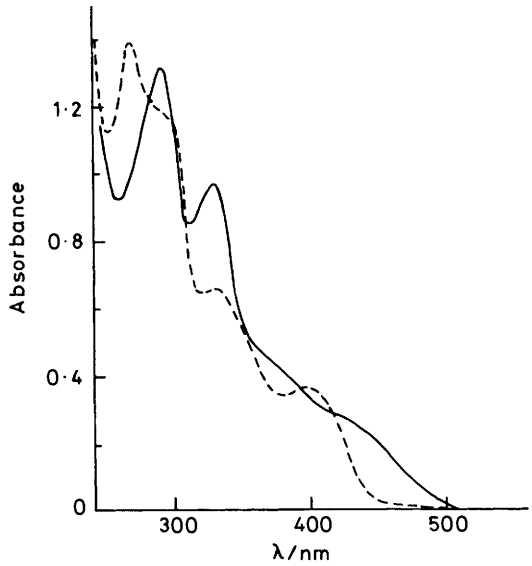
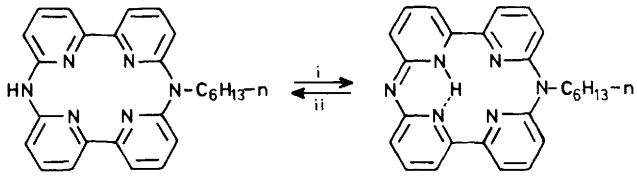


Figure. Absorption spectra of the mono-*N*-n-hexyl macrocycle (5×10^{-5} mol dm^{-3}) at 20 °C: ——— in chloroform, - - - - - - - in methanol



Scheme 3. *Reagents:* i, $CHCl_3$; ii, MeOH

Experimental

M.p.s were measured using a micro melting point measuring apparatus (Yazawa Co., Ltd.) and are uncorrected. I.r. spectra were recorded with a JASCO IRA-1 spectrophotometer. Absorption spectra were recorded with a JASCO UVIDEC-505 spectrophotometer. ^1H N.m.r. spectra were measured for solutions in $CDCl_3$ or CD_3OD with a JEOL-MH 100 spectrometer, and chemical shifts are reported in p.p.m. from internal tetramethylsilane. The mass spectra were recorded with a Hitachi RMU-7L high resolution mass spectrometer.

6,6′-Dibromo-2,2′-bipyridine (**2**).—Compound (**2**) was prepared by the literature method[4] (61%), m.p. 225—226 °C (lit.,[4] 226—227 °C).

6,6′-Diamino-2,2′-bipyridine (**3**).—Compound (**2**) (3.0 g, 9.6 mmol) was placed in one glass ampoule, liquid ammonia (30 g) in another ampoule, and the unsealed ampoules were placed in a 500-ml autoclave, and heated up to 220 °C. The inner pressure rose to 100 kg cm^{-2}, and heating was continued for a further 6 h. After the reaction, the solid in the glass ampoule was dissolved in dilute aqueous HCl (50 ml) and filtered in order to remove insoluble products and any unchanged starting material.

Aqueous ammonia was then added to the filtrate and the precipitated solid collected by filtration, washed with aqueous ammonia and water, and dried under *in vacuo*. The crude product was sublimed *in vacuo* (2 mmHg, 150—200 °C) to give purified product (**3**) (1.42 g, 80%), m.p. 185—186 °C) (lit.,[8] 186 °C) (Found: C, 64.7; H, 5.2; N, 30.2. Calc. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1%).

3H,10H-*Tetrapyrido*[2,1,6-de:2′,1′6′-gh:2″,1″,6″-kl:2‴,-1‴,6‴-na][1,3,5,8,10,12]*hexa-azacyclotetradecine* (**1**).—*Method A*. 6,6′-Diamino-2,2′-bipyridine (**3**) (0.5 g) was dissolved in aqueous 2M-HCl (10 ml), and the solution evaporated to give a yellow salt of (**3**). The salt and an equimolar amount of (**3**) (0.5 g) were placed in an ampoule. The ampoule was sealed under nitrogen and heated at 220 °C for 8 h. The solid in the ampoule was then dissolved in dilute aqueous HCl, and the solution was filtered in order to remove any insoluble material. Aqueous ammonia was added to the filtrate and the precipitate was collected by filtration, washed with aqueous ammonia and water, and dried *in vacuo*. After the removal of the unchanged starting material by sublimation (1 mmHg, 250—300 °C), compound (**1**) was obtained in a pure form (0.84 g, 93%), m.p. 460 °C (decomp.) [lit.,[3] 460 °C (decomp)] (Found: M^+, 338.1271. Calc. for $C_{20}H_{14}N_6$: M^+, 338.1280).

Method B. Compound (**3**) (0.5 g) and an equimolar amount of compound (**2**) (0.84 g) were placed in an ampoule. The ampoule was sealed under nitrogen and heated at 220 °C for 8 h. After purification as in method A, compound (**1**) was obtained in a pure form (0.83 g, 92%).

Method C. 6,6′-Dibromo-2,2′-bipyridine (**2**) (3.0 g, 9.6 mmol) was placed in a glass ampoule. The ampoule, unsealed, was placed in an autoclave (500 ml) and ammonia gas was introduced at room temperature. The pressure was adjusted to be 10 kg cm^{-2} at room temperature, then the autoclave was heated for 8 h at 220—230 °C, when the inner pressure rose to 20 kg cm^{-2}. After the reaction, the solid in the glass ampoule was treated as in method A to give compound (**1**) (1.45 g, 90%).

10-*Hexyl*-3H,10H-*tetrapyrido*[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**).—The macrocycle (**1**) (0.5 g) was dispersed in dioxane (20 ml). Tetra-n-butylammonium bromide (0.5 g) and sodium hydroxide (0.3 g) was added to the suspension and it was heated under reflux until the colour became reddish (about 30 min). Then n-hexyl bromide (2 ml) was added to the reaction mixture and heating was continued for a further 4 h. After the reaction, the solvent was removed by evaporation, and the residue was washed with dilute aqueous sodium hydroxide and then with aqueous ammonia, and dried *in vacuo*. The residue was dissolved in chloroform and separated by column chromatography (alumina–chloroform) to give compound (**4**) (0.47 g, 75%) as a yellow *powder*, m.p. 158—160 °C (Found: C, 74.1; H, 6.3; N, 20.0%; M^+, 422.2129. $C_{26}H_{26}N_6$ requires C, 73.9; H, 6.2; N, 19.9%; M^+, 422.2222); δ_H (100 MHz; [$^2H_4$]methanol) 7.72 (2 H, t, 4-H py), 7.56 (2 H, t, 4′-H py), 7.35 (2 H, d, 3-H py), 7.12 (2 H, d, 3′-H py), 7.02 (2 H, d, 5-H py), 6.85 (2 H, d, 5′-H py), 3.96 (2 H, br t, NCH_2), 1.73 (2 H, br s, $NCCH_2$), 1.32 (6 H, br s, CH_2), and 0.88 (3 H, br t, CH_3); δ_H (100 MHz; $CDCl_3$) 16.9 (1 H, s, NH), 7.68—6.91 (12 H, m, py), 3.98 (2 H, br t, NCH_2), 1.82 (2 H, br s, $NCCH_2$), 1.38 (6 H, br s, CH_2), and 0.90 (3 H, br t, CH_3).

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Received 15*th December* 1983; *Paper* 3/2208