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Nucleophilic Attack upon Coordinated Heterocycles; Definitive Evidence for the Enhanced Electrophilicity of Coordinated Pyridines

EDWIN C. CONSTABLE

University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW, U.K.

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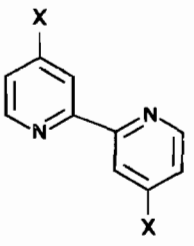
The complex $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2$ (Cl_2-bipy = 4,4'-dichloro-2,2'-bipyridine) has been prepared, and its reactions with nucleophiles investigated. The complex is very susceptible to reaction with nucleophiles, and gives high yields of complexes $[Ru(bipy)_2L]^{n+}$ (L = 4,4'-disubstituted 2,2'-bipyridine). These reactions occur considerably more rapidly than those of the uncomplexed ligand, and provide direct evidence for the activation of pyridine based heterocycles towards nucleophilic attack by coordination to a metal ion.

Introduction

The interaction of a metal ion with a ligand is known to cause a perturbation of the metal-centred orbital energy levels. This assumption is at the basis of ligand field theory, and has an accumulation of experimental observation to support it [1–3]. It is also evident that coordination to a metal ion must also have a similar critical effect upon the molecular orbitals of the ligand, although this aspect of the metal–ligand interaction has not been so widely investigated. Williams has reported INDO molecular orbital calculations for a range of six-membered ring heterocycles and their iron(II) complexes, and these provide some evidence for the anticipated electronic perturbation within the ligand [4]. Specifically, the 2- and 4-positions (with respect to the ring nitrogen atom) were found to be activated towards nucleophilic attack, an observation corresponding to a lowering in energy of the LUMO at these positions [5]. The activation of these positions towards attack by nucleophiles was initially proposed by Gillard [6], on the basis of an analogy between a metal complex of a heterocycle and its quaternary salts. Gillard has investigated the interaction of nucleophiles with a range of complexes incorporating heterocyclic ligands, and has presented evidence for attack at the 2- and 4-positions, although these reports have attracted some controversial discussion [7, 8]. The majority of the studies reported by Gillard have been concerned with unsubstituted heterocyles, in which the product is a coordinated dihydropyridine. Such species are expected to be unstable, and in the absence of a reaction pathway allowing the hydride ion to act as a leaving group, or an oxidative dehydrogenation, tend to undergo elimination of the nucleophile to regenerate the starting complex. The net effect is that the equilibrium concentration of the coordinated dihydropyridine is expected to be very low.

Although the reactions of coordinated 5-nitro-1,10-phenanthroline [7] and 5-chloro-1,10-phenanthroline [9, 10] have been extensively investigated, there have been few studies of complexes in which a substituent is attached directly to the heterocyclic ring. If such a substituent were a good leaving group, stabilisation of the dihydropyridine intermediate by coordination to the metal ion might be expected to favour the AE mechanism [11]. Reactions of this type are of particular interest in the light of recent spectroscopic [12] and chemical [13–15] observations indicating a novel reactivity associated with the 3- and 3'-positions of coordinated 2,2'-bipyridines. As part of a more extensive investigation into the reactions of coordinated ligands [12, 13, 16], the interaction of nucleophiles with complexes containing coordinated 4,4'-dichloro-2,2'-bipyridine (*1a*)* were studied, and it is these results which are reported herein.



1a) X = Cl

1b) X = EtO

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*Throughout, the abbreviations bipy and X_2bipy are used to mean 2,2'-bipyridine and 4,4'-diX-substituted-2,2'-bipyridine, respectively.

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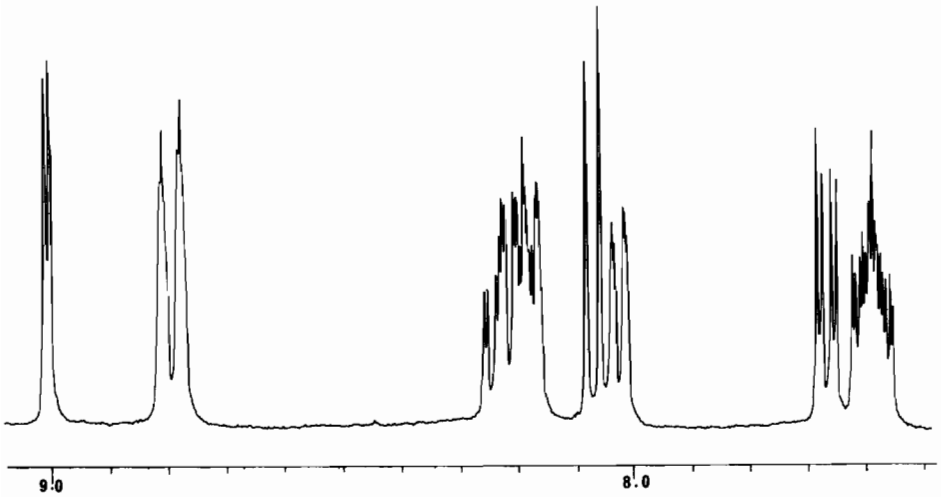


Fig. 1. 250 MHz ^{1}H n.m.r. spectrum of $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2$; 20 mg in 0.5 ml CD_3COCD_3; 25 °C, 100 transients, 70° pulse, Gaussian multiplied.

Results and Discussion

4,4′-Dichloro-2,2′-bipyridine was prepared from 2,2′-bipyridine by a four-step reaction sequence; 2,2′-bipyridine → 2,2′-bipyridine N,N′-dioxide → 4,4′-dinitro-2,2′-bipyridine N,N′-dioxide → 4,4′-dichloro-2,2′-bipyridine N,N′-dioxide → 4,4′-dichloro-2,2′-bipyridine [17–19]. The reaction of 4,4′-dichloro-2,2′-bipyridine with $[Ru(bipy)_2Cl_2]$ [20] in boiling ethanol led to the formation of a deep red solution, from which a near quantitative yield of the deep red complex $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2 \cdot H_2O$ was obtained upon the addition of an excess of $[NH_4](PF_6)$. The ^{1}H n.m.r. spectrum of this complex is shown in Fig. 1, and clearly exhibits a low field doublet (J = 2.0 Hz) at δ 9.00, which may be assigned to $H_{3,3}$, of the Cl_2bipy ligand [12]. Homonuclear decoupling experiments established the assignment of the $H_{5,5}$, and $H_{6,6}$, resonances of the Cl_2bipy ligand at δ 7.65 (J = 6.1 and 2.0 Hz) and δ 8.05 (J = 6.1 Hz) respectively. The introduction of the substituted bipy ligand results in a lowering of the molecular symmetry from the D_{3h} observed in $[Ru(bipy)_3]^{2+}$ [21], and this is observed in the splitting of the ABCD pattern of resonances arising from the bipy ligands in $[Ru(bipy)_2(Cl_2bipy)]^{2+}$ into two subsets. A similar effect is observed in the ^{1}H n.m.r. spectra of other $[Ru(bipy)_2X_2]^{2+}$ complexes, and of $[Ru(bipy)_2Cl_2]$ [22].

Treatment of an ethanolic solution of $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2$ with Na(OEt) led to the quantitative formation of a 4,4′-diethoxy-2,2′-bipyridine (*1b*) complex, isolated as the hexafluorophosphate salt $[Ru(bipy)_2\{(EtO)_2bipy\}](PF_6)_2 \cdot 2H_2O$. The ^{1}H n.m.r. spectrum of this complex is illustrated in Fig. 2, and it is immediately evident that the low field resonance assigned to $H_{3,3}$, of the Cl_2bipy has been replaced by

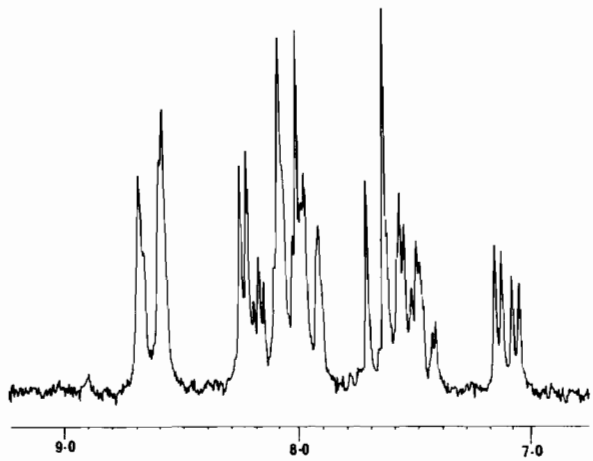


Fig. 2. 80 MHz ^{1}H n.m.r. spectrum of the aromatic region of $[Ru(bipy)_2(EtO_2bipy)](PF_6)_2$; 25 mg in 0.5 ml CD_3COCD_3; 33 °C, 160 transients, 90° pulse.

a similar doublet (J = 2.1 Hz) at δ 8.35. Similar upfield shifts are experienced by the resonances due to $H_{5,5}$, and $H_{6,6}$, of the $(EtO)_2$bipy ligand, which now appear at δ 7.10 and δ 7.74 respectively. The CH_3 and CH_2 protons of the ethoxy group are observed as a triplet at δ 1.43 and a quartet at δ 4.35 respectively. The electronic spectra of the complexes show changes also, with a shift in λ_{max} from 444 nm in the case of $[Ru(bipy)_2(Cl_2bipy)]^{2+}$ to 460 nm for the $(EtO)_2$bipy complex. Fig. 3 shows the effect upon the visible region electronic spectrum of an ethanolic solution of $[Ru(bipy)(Cl_2bipy)](PF_6)_2$ of the addition of excess Na(OEt); the formation of $[Ru(bipy)_2\{(EtO)_2bipy\}]^{2+}$ is accompanied by the occurrence of isosbestic points at 425 nm and 478 nm. The changes in λ_{max} are associated with the differing σ-donor and π-acceptor properties of the ligands, and have been discussed in detail by Seddon [23]. The spectra reproduced in

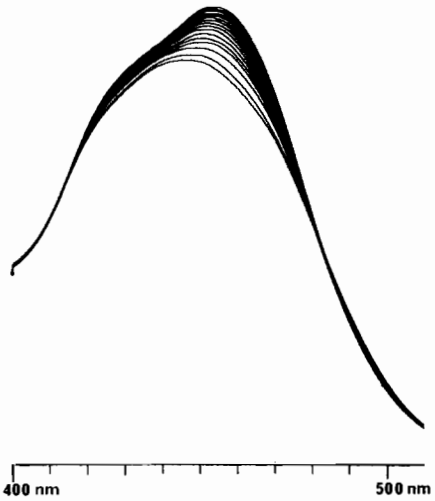
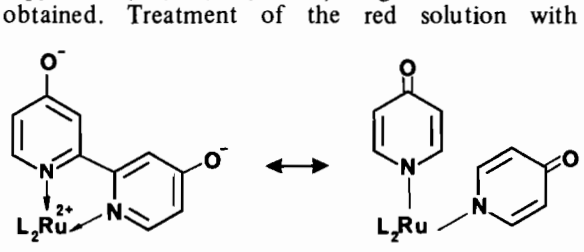


Fig. 3. Electronic spectrum of $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2$ in ethanol, showing the effect of the addition of sodium ethoxide. The lower trace is that due to the starting complex. The spectra were recorded over 5 minutes at room temperature, after which time no further spectral changes occurred.

Fig. 3 were recorded over 5 minutes at room temperature, after which period the reaction was complete, and no further changes occurred. In contrast, 4,4′-dichloro-2,2′-bipyridine was recovered unchanged after heating to reflux with excess sodium ethoxide in ethanol for 20 minutes. The best conditions for the preparation of 4,4′-diethoxy-2,2′-bipyridine involved treatment of the dichloro-compound with excess sodium ethoxide in dmf solution [24].

A similar substitution reaction occurred on heating aqueous solutions of $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2$ with sodium hydroxide, when a bright red solution containing $[Ru(bipy)_2(O_2bipy)]$ was obtained. This solution gave no precipitate on treatment with $[NH_4](PF_6)$, $Na(BPh_4)$ or $Na(BF_4)$, and it was concluded that the neutral complex (*2a* ⟷ *2b*) of the deprotonated 4,4′-dihydroxy-2,2′-bipyridine (2,2′-bipyridin-4(1*H*),4′(1′*H*)-dione) ligand had been obtained. Treatment of the red solution with



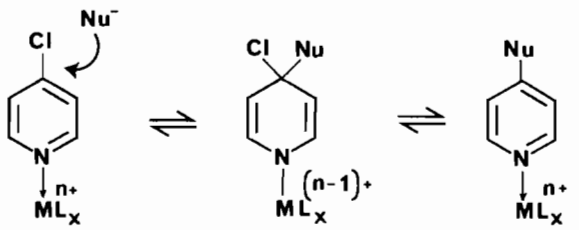
2a *2b*

hexafluorophosphoric acid led to an immediate precipitation of the red salt $[Ru(bipy)_2(HO_2bipy)](PF_6)_2 \cdot 1.5H_2O$. This complex is of interest in providing a pyridone in the tautomeric 4-hydroxypyridine form, and the chemistry of complexes of this type is that of a phenol, rather than an amide. Thus, there are marked changes in the ^1H n.m.r. and electronic spectra upon the addition of bases to aqueous solutions. In particular, the electronic spectrum of aqueous solutions of $[Ru(bipy)_2\{(HO)_2bipy\}]^{2+}$ shows λ_{max} at 457 nm, which shifts to 464 nm upon the addition of hydroxide, a change which is fully reversible upon acidification. These changes in λ_{max} are associated with the formation of isosbestic points at 405 and 472 nm.

The complex $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2$ also reacted very rapidly with sodium sulphite in aqueous conditions, to give deep red solutions containing $[Ru(bipy)_2\{(NaO_3)_2bipy\}]^{2+}$, from which the complexes $[Ru(bipy)_2\{(O_3S)_2bipy\}]$, $[Ru(bipy)_2\{(HO_3S)_2bipy\}](PF_6)_2$ or $[Ru(bipy)\{(O_3S)_2bipy\}](PF_6)_2$ could be obtained after chromatography over Sephadex LH-20. These complexes were identical to those obtained by the reaction of $[Ru(bipy)_2Cl_2]$ with 2,2′-bipyridine-4,4′-disulphonic acid [25]. These complexes are of particular interest as they are very soluble in water, and provide a source of neutral or anionic *tris* diimine complexes. This route to these complexes, giving the desired sulphonic acid compound directly, is a considerable improvement over the previous syntheses, which involved a tedious isolation of the free ligand, 2,2′-bipyridine-4,4′-disulphonic acid, in a five step synthesis from 2,2′-bipyridine [25]. 4,4′-Dichloro-2,2′-bipyridine was recovered unchanged after heating to reflux with aqueous ethanolic solutions of sodium sulphite or sodium hydrogen sulphite for prolonged periods.

No reaction occurred when $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2$ was heated to reflux with aqueous solutions of sodium nitrite, or on its own in ethanol. Heating to reflux with ethanolic solutions containing n-propylamine or n-butylamine led to the formation of mixtures of the 4-alkylamino and 4-ethoxy substituted compounds. No reaction occurred when $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2$ was heated to reflux with n-propylamine in acetone or acetonitrile for 10 minutes.

The observations described above demonstrate clearly that the coordination of 4,4′-dichloro-2,2′-bipyridine to ruthenium(II) results in a considerable activation of the molecule towards nucleophilic attack. The most likely mechanism for the substitution involves nucleophilic attack at C_4 to produce a 1,4-dihydropyridyl anion, stabilised by coordination to the metal ion. Loss of chloride ion results in rearomatisation, with concomitant formation of the substitution product (Scheme 1). The degree of activation awaits accurate kinetic studies of the reaction, but on an empirical basis it is evident that it is very marked. Our spectroscopic measurements indicate that substitution at both pyridyl rings occurs concurrently, and that formation of the 1,4-dihydro species is rapid and complete, although detailed



Scheme 1

kinetic studies are required before such a conclusion can be reached. The complex $[Ru(bipy)_2(Clbipy)](PF_6)_2$ (Clbipy = 4-chloro-2,2′-bipy) shows similar substitution reactions, and a comparison of the kinetics for this complex with those for the 4,4′-dichloro complex may provide evidence for the reaction sequence. However, these results establish the enhanced electrophilicity associated with a coordinated pyridine, predicted by Gillard [6] and Williams [4], although they do not, of course, establish the position of equilibrium in the case of unsubstituted ligands.

Experimental

All reactions were conducted under an atmosphere of dry nitrogen. Sodium sulphite, sodium hydroxide and ammonium hexafluorophosphate were used as supplied (B.D.H.). 2,2′-Bipyridine (Aldrich) was recrystallised from petroleum ether before use, and stored in a dark vessel *in vacuo*. $[Ru(bipy)_2Cl_2]$ [20], 4,4′-dichloro-2,2′-bipyridine [17–19] and $[Ru(bipy)_2\{(NaO_3S)_2bipy\}](PF_6)_2$ [25] were prepared by the literature methods and had satisfactory ^1H n.m.r. and mass spectra, and elemental analyses.

^1H n.m.r. spectra were recorded on Bruker WH-400 or WM-250 or Varian CFT-20 spectrometers. Electronic spectra were recorded on a Pye-Unicam PU 8800 spectrophotometer using 10 mm cells.

Bis(2,2′-bipyridine)(4,4′-dichloro-2,2′-bipyridine)-ruthenium(II) Hexafluorophosphate

$[Ru(bipy)_2Cl_2]$ (484 mg, 1 mmol) and 4,4′-dichloro-2,2′-bipyridine (225 mg, 1 mmol) were heated to reflux in ethanol (250 ml) for 20 h, after which time a clear red solution had been obtained. This solution was filtered hot, and treated with a solution of ammonium hexafluorophosphate (1 gm) in methanol (20 ml), and allowed to cool, when red crystals were obtained (900 mg, 97%). Recrystallisation from 95% ethanol gave small red plates of $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2 \cdot H_2O$ (Found: C, 37.91; H, 2.45; N, 8.70%. Calc. for $C_{30}H_{24}N_6Cl_2F_{12}OP_2Ru$: C, 38.05; H, 2.54; N, 8.88%).

Bis(2,2′-bipyridine)(4,4′-bisethoxy-2,2′-bipyridine)-ruthenium(II) Hexafluorophosphate

A: $[Ru(bipy)_2(Cl_2bipy)](PF_6)_2 \cdot H_2O$ (57 mg, 0.06 mmol) was added to a solution of sodium ethoxide prepared by the addition of sodium (25 mg, 1.1 mmol) to ethanol (12 ml), and the solution so obtained heated to reflux for 30 min, after which period the reaction mixture was quenched in water (30 ml) and treated with ammonium hexafluorophosphate (1 gm), when orange needles were precipitated (59 mg, 100%). Recrystallisation of the orange solid from aqueous ethanol (1:1) gave bright orange needles of $[Ru(bipy)_2\{(EtO)_2bipy\}](PF_6)_2 \cdot 2H_2O$ (Found: C, 41.51; H, 3.68; N, 8.65% Calc. for $C_{34}H_{36}N_6F_{12}O_4P_2Ru$: C, 41.51; H, 3.66; N, 8.54%).

B: $[Ru(bipy)_2Cl_2]$ (48.4 mg, 0.1 mmol) and 4,4′-bisethoxy-2,2′-bipyridine (25 mg, 0.1 mmol) [24] were dissolved in ethanol (25 ml) and the solution heated to reflux for 24 h, after which period a red solution had been obtained. Treatment of this solution with ammonium hexafluorophosphate (100 mg) followed by the addition of water (30 ml) led to the precipitation of $[Ru(bipy)_2\{(EtO)_2bipy\}](PF_6)_2 \cdot 2H_2O$ identical in all respects to that prepared by method A.

Attempted Reaction of 4,4′-dichloro-2,2′-bipyridine with Sodium Ethoxide

4,4′-Dichloro-2,2′-bipyridine (100 mg, 0.44 mmol) was heated to reflux with a solution of sodium ethoxide (prepared by the addition of 100 mg of sodium to 15 ml ethanol) for 20 min, after which period the reaction mixture was quenched in water (50 ml). The white solid precipitated was dried and examined by ^1H n.m.r.; the spectrum was identical to that of a solution of 4,4′-dichloro-2,2′-bipyridine.

Bis(2,2′-bipyridine)(2,2′-bipyridin-4,4′-olato-N,N′-(2-))ruthenium(II) and Bis(2,2′-bipyridine)(4,4′-bishydroxy-2,2′-bipyridine)ruthenium(II) Hexafluorophosphate

$[Ru(bipy)_2(Cl_2bipy)](PF_6)_2 \cdot H_2O$ (70 mg, 0.074 mmol) and sodium hydroxide (80 mg, 2 mmol) were dissolved in water (18 ml) and the solution so obtained heated to reflux for 30 min, to give a deep red solution. This was filtered hot, and treated with aqueous hexafluorophosphoric acid (0.5 ml, 40%), when an orange microcrystalline precipitate slowly formed. This was collected by filtration, dried, and recrystallised from aqueous ethanol to give orange plates of $[Ru(bipy)_2\{(HO)_2bipy\}](PF_6)_2 \cdot 1.5H_2O$ (Found: C, 39.07; H, 2.76; N, 8.99%. Calc. for $C_{30}H_{27}N_6F_{12}O_{3.5}P_2Ru$: C, 39.21; H, 2.94; N, 9.15%).

Disodium Bis(2,2′-bipyridine)(4,4′-disulphonato-2,2′-bipyridine-N,N′)ruthenium(II) Hexafluorophosphate

$[Ru(bipy)_2(Cl_2bipy)](PF_6)_2 \cdot H_2O$ (70 mg, 0.074 mmol) and sodium sulphite heptahydrate (0.5 gm)

were dissolved in water (20 ml) and the solution heated to reflux for 30 min, after which period the solution was concentrated to 5 ml, and allowed to cool. Sodium salts were removed by filtration, and the filtrate treated with sodium hexafluorophosphate (0.5 gm). The red solution was then chromatographed over Sephadex LH-20, using water as eluant, when a single red band passed down the column. This was collected, and dried *in vacuo* to give a deep red solid, possessing identical ^{1}H n.m.r., uv/vis and infra-red spectra to an authentic sample of $Na_2[Ru(bipy)_2\{(O_3S)_2bipy\}](PF_6)_2$ prepared by the reaction of $[Ru(bipy)_2Cl_2]$ with 2,2′-bipyridine-4,4′-disulphonic acid [25].

Attempted Reaction of 4,4′-dichloro-2,2′-bipyridine with Sulphite

A: 4,4′-Dichloro-2,2′-bipyridine (100 mg, 0.44 mmol) was heated to reflux with a solution of sodium sulphite heptahydrate (1 gm) in water (10 ml) and ethanol (10 ml) for 2 h. After this period the ethanol was removed *in vacuo*, and the aqueous suspension extracted with chloroform (3 × 10 ml). The chloroform extracts were combined and dried over magnesium sulphate, and evaporated *in vacuo* to give 4,4′-dichloro-2,2′-bipyridine (98 mg) with identical properties to an authentic sample. The aqueous solution, after chloroform extraction did not give a red coloration on treatment with iron(II) salts.

B: 4,4′-Dichloro-2,2′-bipyridine (100 mg) was also recovered unreacted after heating to reflux with a solution of sodium hydrogen sulphite, prepared by saturating an aqueous solution of sodium hydroxide (0.4 gm in 10 ml) with sulphur dioxide.

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