A Simple Example of the Fluxional Behaviour of Ruthenium-Coordinated C_2-Symmetric Monodentate Ligands − Synthesis, ^{1}H NMR Spectroscopic Study, and Crystal Structure of *cis*-[Ru(bpy)$_2$(4Pic)$_2$](PF$_6$)$_2$

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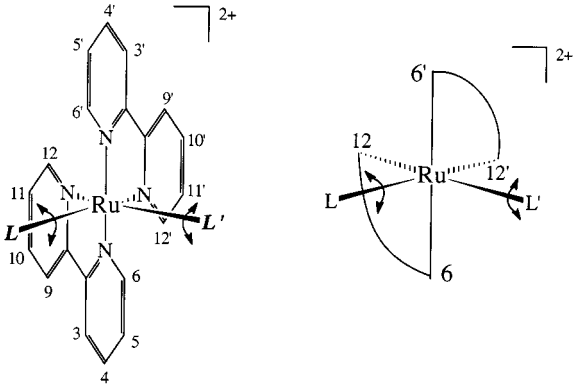
In complexes of the type *cis*-[Ru(bpy)$_2$(L)$_2$](PF$_6$)$_2$ the fluxional behaviour (dynamics of rotation) of the monodentate heterocyclic ligands (L) in solution can be well investigated with ^{1}H NMR spectroscopy. As both the *cis*-[Ru(bpy)$_2$] moiety and the coordinated 4-picoline have a C_2 symmetry, no atropisomers of *cis*-[Ru(bpy)$_2$(4Pic)$_2$](PF$_6$)$_2$ are possible, and as a result a relatively easily understandable ^{1}H NMR spectrum is observed. The fast and slow rotation of the 4-picoline ligands have been monitored using variable-temperature 1D and 2D ^{1}H NMR spectroscopy. In addition the room temperature, solid state, X-ray structure is presented.

Introduction

The investigation of the coordinative and fluxional behaviour (dynamics of rotation) of metal-coordinated heterocyclic ligands is important for the understanding of the biological functions and activity of transition metal ions in living systems.[1,2] The solid-state and solution studies on platinum compounds with *cis* bifunctionally coordinated DNA (model) bases, have provided an enormous insight into the activity of these kinds of antitumour complexes on a molecular level.[3,4] Ruthenium complexes which are currently under investigation for their potential use as antitumour agents [2,5] are mostly octahedral six-coordinated complexes; the *cis* bifunctional coordination of heterocyclic ligands is therefore different from square-planar platinum complexes and is as yet not well understood. The ruthenium(II) antitumour complex *cis*-[Ru(dmso)$_4$Cl$_2$] was the first suitable system to study the coordinative and fluxional behaviour of *cis bis*-adducts of the type *cis*-[Ru(dmso)$_2$Cl$_2$(L)(L′)] with L and L′ being heterocyclic N-donor ligands.[6−12] The recent finding that structurally similar *cis*-dichlororuthenium(II) complexes of the type *cis*-[Ru(LL′)$_2$Cl$_2$] {in which LL′ is a chelating N-donor ligand like 2,2′-bipyridine[13] or 2-(phenyl)azopyridine[14]} show very different biological activity, inspired us to investigate in detail the coordination and the fluxional behaviour of monodentate heterocycles in the complexes of the type *cis*-[Ru(LL′)$_2$(L)$_2$](PF$_6$)$_2$.



Scheme 1. Structural (left) and schematic (right) representation of the A enantiomer of the *cis*-[Ru(bpy)$_2$(L)$_2$]$^{2+}$ system and proton numbering scheme of the bpy

In the complexes *cis*-[Ru(bpy)$_2$(L)$_2$](PF$_6$)$_2$ (Scheme 1), in which the L's are imidazole-type ligands, the ligands can flip around their Ru−N axis, either fast or slowly on the NMR timescale, depending on the size of the substituents on the imidazole ring and on the temperature.[15,16] With the relatively small 1-methylimidazole (MeIm), the ^{1}H NMR spectrum of the complex shows fast rotation of the monodentate ligands at all the measured temperatures. The sterically more demanding 1,2-dimethylimidazole (Me2Im) and 1-methylbenzimidazole (MeBim) are fast rotating on the ^{1}H NMR timescale, at temperatures above room temp.,

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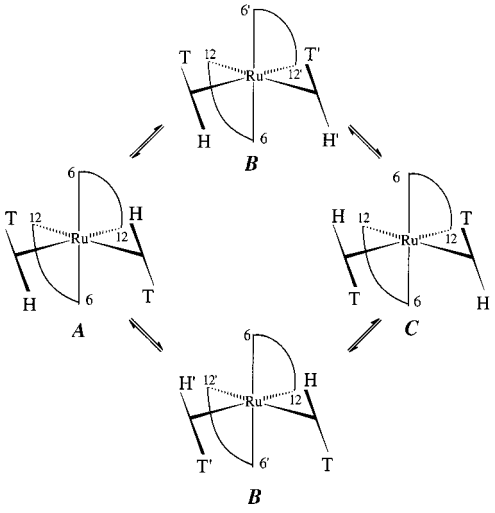
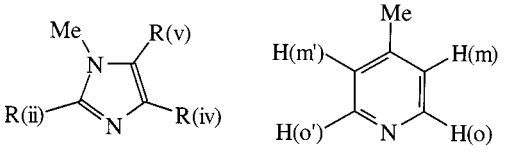
but are relatively slow rotating at temperatures below 0 °C.[15,16]

1-Methylimidazole, 1,2-dimethylimidazole, and 1-methylbenzimidazole are so-called lopsided ligands of which one site can be defined as the head (H) and the other as the tail (T). In octahedral sites, lopsided ligands can theoretically orient in 4 staggered positions, but in practice usually only one orientation is preferential. In *cis*-$[Ru(bpy)_2(L)_2](PF_6)_2$ (L = imidazole ligand) two staggered orientations are not accessible because of the steric bulk of the bidentate bpy; however, the imidazole ligands do occur in the other two orientations on the ruthenium. All the resulting four possible atropisomers have been observed and identified for the Me_2Im and MeBim complexes: two head-to-head (HH) isomers (which have the corresponding atoms of the imidazole at the same site of the N−Ru−N plane) and two head-to-tail (HT) isomers (in which the corresponding atoms of the imidazole ligands are at opposite sites of the N−Ru−N plane) (Scheme 2).[15,16] The two HT isomers, A and C, both have a twofold symmetry axis which causes the two bpy ligands and the two imidazole ligands to be identical and indistinguishable with ^{1}H NMR spectroscopy. Due to the twofold symmetry in the *cis*-$[Ru(bpy)_2]$ moiety, the hypothetical HH atropisomers, B and B′, are identical to each other; the HH orientation of the lopsided monodentate ligands causes the two bpy ligands in these atropisomers to be inequivalent, as can be observed with ^{1}H NMR spectroscopy. In general, the presence of atropisomers causes complex, but interesting spectra; therefore the use of a relatively simple system with high symmetry is important for a detailed understanding of the data.



Scheme 2. Schematic representation of the 4 possible atropisomers of the A enantiomer of the *cis*-$[Ru(bpy)_2(L)_2]_2$, system. For L = 4-picoline these atropisomers all become identical

In the present study the synthesis and room temperature, solid state, X-ray structure of the high-symmetry molecule *cis*-$[Ru(bpy)_2(4Pic)_2](PF_6)_2$ (**1**) is described and the fluxional behaviour of the 4-picoline (4Pic) ligands in solution



Scheme 3. Structural representation and proton numbering scheme of 1-Methylimidazoles (left) and 4-picoline (right)

is discussed. The rod-like 4Pic ligand coordinates via the N-atom, and therefore is not a lopsided ligand like the methylimidazole ligands (Scheme 3). The CH_3 groups of the 4Pic ligand rotate rapidly making the ligand rod like. Due to the three twofold symmetry axes present in complex **1** {one for the *cis*-$[Ru(bpy)_2]$ moiety and one for each Ru-picoline moiety}, no atropisomers of *cis*-$[Ru(bpy)_2(4Pic)_2](PF_6)_2$ are possible, resulting in fully interpretable ^{1}H NMR spectroscopic data.

Results and Discussion

Solid-State Structure

The *cis*-$[Ru(bpy)_2]$ moiety is chiral, and in the crystal structure of I both the A and A enantiomers have been found in the unit cell (complex A and B). In Figure 1 the molecular structure of one of the two symmetry-independent enantiomers is reported together with the atom numbering. The most significant geometrical parameters are summarized in Table 1. The structure of each enantiomer shows a six-coordinated pseudo-octahedral ruthenium ion with all ligands in a *cis* configuration. The Ru−N bond lengths for the bpy ligands in the two *cis*-$[Ru(bpy)_2(4Pic)_2]^{2+}$ moieties range from 2.042(4) to 2.084(4) Å and are significantly shorter than those involving the 4Pic ligands [2.103(4) to 2.122(4) Å]. These values are quite similar to those in *cis*$[Ru(bpy)_2(L)_2](BF_4)_2$, where

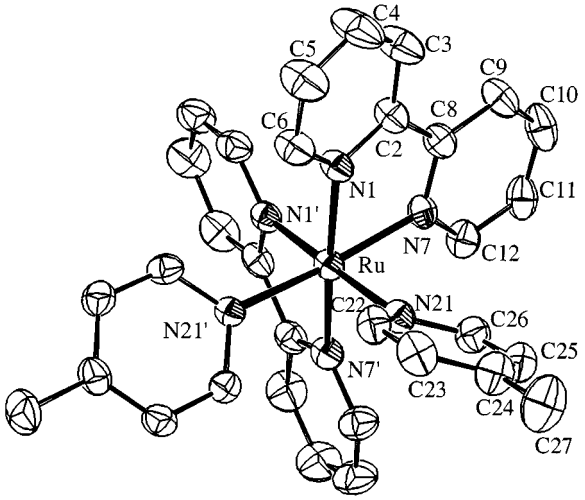


Figure 1. Thermal ellipsoid plot of one of the A enantiomers of 1. The PF_6^- anions, co-crystallised solvent molecules and protons are omitted for clarity. The view is approximately the same as in Schemes 1 and 2. Relevant data are given in Tables 1 and 2

Table 1. Selected bond lengths [Å] and bond angles [°] for the two independent complex units A and B of *cis*-$[Ru(bpy)_2(4Pic)_2](PF_6)_2$

	Complex A	Complex B
Rul−N7	2.060(4)	2.042(4)
Rul−Nl	2.084(4)	2.061(4)
Rul−Nl′	2.070(4)	2.073(4)
Rul−N7′	2.056(5)	2.053(5)
Rul−N21	2.103(4)	2.122(4)
Rul−N21′	2.104(5)	2.108(4)
N7−Rul−N1	78.7(2)	78.9(2)
Nl−Rul−N21	97.6(2)	99.1(2)
Nl′−Rul−N21	87.6(2)	85.6(2)
N7−Rul−Nl′	96.0(2)	96.2(2)
N7−Rul−N21′	90.4(2)	90.1(2)
Nl−Rul−N21′	84.9(2)	88.0(2)
Nl′−Rul−N21′	99.0(2)	98.3(2)
N21−Rul−N21′	90.6(2)	91.7(2)
N7−Ru I−N7′86.4(2)	87.1(2)	
N1−Rul−N7′	96.7(2)	94.3(2)
Nl′−Rul−N7′	79.1(2)	79.1(2)
N21−Rul−N7′	92.8(2)	91.2(2)
N7−Rul−N21	176.2(2)	177.2(2)
N1−Rul−Nl′	173.5(2)	172.1(2)
N7′−Rul−N21′	176.0(2)	175.9(2)

the Ru−N bond lengths range from 2.04 to 2.05 Å for the bpy ligands and from 2.09 to 2.10 Å for the Im ligands.[17] Labelling the bpy involving the N1 and N7 as bpy#1, that involving the Nl′ and N7′ as bpy#2, the 4-picoline involving N21 as 4Pic#1 and the 4-picoline involving the N21′ as 4Pic#2, the mean values of the dihedral angles between the least-squares plane through the ligands in the two *cis*-$[Ru(bpy)_2(4Pic)_2]^{2+}$ complexes are: 58.9(2)° (bpy#1−4Pic#1), 85.6(1)° (bpy#1−4Pic#2), 84.3(2)° (bpy#2−4Pic#1), 46.8(1)° (bpy#2−4Pic#2), 79.3(1)° (bpy#l-bpy#2) and 59.5(1)° (4Pic#1−4Pic#2).

In conclusion, in both *cis*-$[Ru(bpy)_2(4Pic)_2]^{2+}$ cations the 4Pic ligands, gauche to each other, are orthogonal only to one bpy, whereas they are tilted with respect to the other bpy on angles which range from 47 to 59°. The bond lengths and angles in the PF_6^- anions and in the acetone solvate molecule are as expected. The *cis*-$[Ru(bpy)_2(4Pic)_2]^{2+}$ cations interact with the PF_6^- anions through an array of CH···F hydrogen interactions.

Solution Structure

The ^{1}H NMR spectrum of **1** in [D_6]acetone at room temp. (Figure 2) shows a total of ten multiplet signals in the aromatic region, four doublets and four triplets of equal intensity and two doublets with an integral value twice as high as that of the other eight multiplets. All resonances could be assigned as shown in Figure 2 on the basis of COSY and NOESY spectra (see Supplementary Material), in a similar way as has been described for the analogous imidazole complexes.[15,16] The fact that the two H(*ortho*) protons [and the two H(*meta*) protons] resonate at the same frequency, indicates that the picolines rotate fast on the NMR timescale around their Ru−N axes. Upon lowering the temperature, the eight bpy signals show a small down-field shift, but remain sharp multiplets over the whole temperature range measured. In contrast, the two 4Pic doublets H(*ortho*) and H(*meta*), at δ = 8.4 and 7.3, respectively, first start broadening on lowering the temperature and finally, both, split up in two doublets at −90 °C separated by 56 and 27 Hz, respectively (Figure 2).

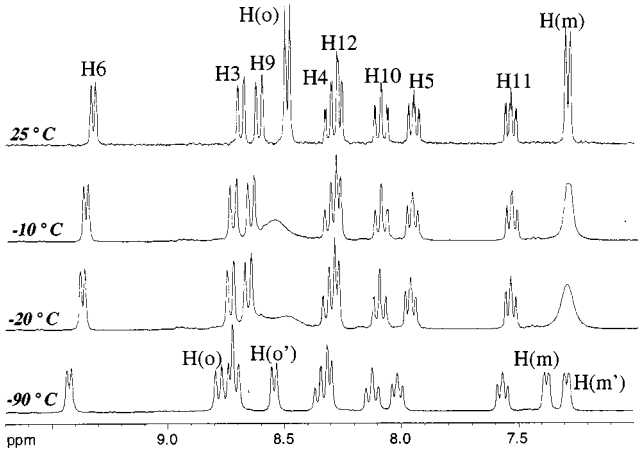


Figure 2. Aromatic region of the ^{1}H NMR spectra of I in [D_6]acetone at room temp., −10, −20, and −90 °C

The fact that the four aromatic 4-picoline protons have become inequivalent at low temperatures, whilst the two bpy ligands and the two picoline ligands remain indistinguishable, indicates that the 4Pic ligands slowly flip by 180° between two orientations, on the NMR timescale, and all four atropisomers depicted in Scheme 2 are present. Due to the symmetries present in the system (which makes the four atropisomers identical and thus indistinguishable) only a total of 12 resonances are found in the aromatic region of the spectrum.

2D NMR techniques like NOESY and **ROESY** are powerful methods for accurately determining the orientation of monodentate ligands in atropisomers and their rotational behaviour (via interligand NOE cross-peaks and exchange cross-peaks). In Figure 3 the aromatic region of a **ROESY** spectrum of I is shown and the most characteristic interligand cross-peaks are indicated. The most down-field shifted H(*ortho*) doublet shows a NOE cross-peak with the bpy H6, as well as the H12 (of the other bpy!) indicating this resonance belonging to the H(o) proton, which is wedged in between the two bpy ligands. The NOE cross-peak of the other H(*ortho*) doublet, H(o′), with only the H6 resonance confirms the assignment of this peak to the 4Pic H(o′) proton which is oriented in between a bpy and the other picoline. The relative down-field shift of the H(o) with respect to the H(o′) signal is nicely explained by the stronger deshielding the former protons experience with respect to the latter. In Figure 4, a space-filling model of I clearly shows the H(o) proton to be wedged in between the two bpy ligands, but not above the (shielding) aromatic pyridine rings. The H(o′) proton is situated close to one bpy on the opposite site with respect to where the H(o) of the other 4Pic is positioned, but in addition, this proton is oriented just above the aromatic ring of the neighbouring pico-

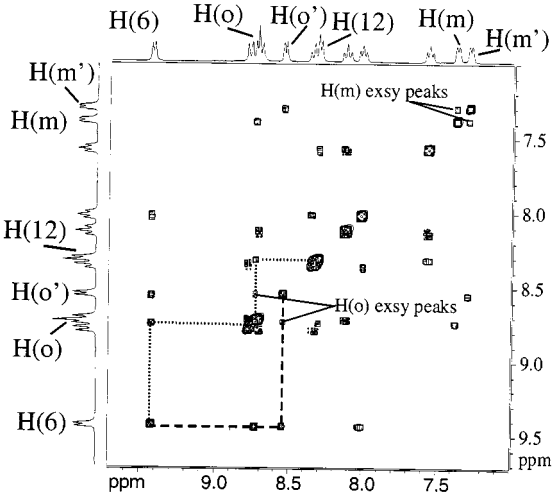


Figure 3. Positive (EXSY) and negative (NOE) level of the aromatic region of the **ROESY** spectrum of I in [D_6]acetone at −100 °C, recorded with a mix time of 500 ms. The H(o)−H6 and H(o)−H12, and the H(o′)−H12 NOE cross-peaks are indicated with a dotted and dashed line, respectively. The observed exchange peaks are between the H(o) and H(o′), and the H(m) and H(m)′ resonances

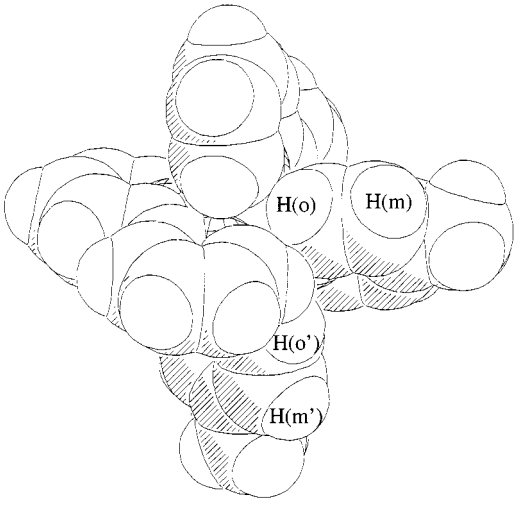


Figure 4. Space-filling representation of the solid state molecular structure of the A enantiomer of the cation of 1. The H(o) proton is clearly wedged in between the H6 site of one bpy and the H12 site of the other bpy, whilst the H(o′) proton is close to the pyridine rings of a bpy as well as the neighbouring 4-picoline

line ligand, which nicely supports the explanation of the relative upfield shift of 0.2 ppm of this proton. However, the solution and solid state orientations of the ligands should, by no means, be considered to be the same by default.

Although the VT ^{1}H NMR spectroscopic data indicate the slowing down of the rotation of the picolines around their Ru−N axes at lower temperatures, the ligands do not stand still on the NMR timescale at the lowest temperature investigated (−100 °C). In Figure 3 the exchange level of the ROESY spectrum is shown in which clear cross peaks are present between the two H(*ortho*) proton signals, H(o) and H(o′), of the picoline and also between the two H(*meta*) proton resonances, H(m) and H(m′). The picoline thus exhibits a greater fluxionality than the bulky MeBim and Me2Im ligands in the analogous complexes, that only show exchange cross-peaks at higher temperatures.[15,16] In practice this means that the four atropisomers of I can interchange even at temperatures as low as −90 to −100 °C, albeit slow on the NMR timescale. Picoline is obviously less hindered in its rotation around its Ru−N axis than are the bicyclic MeBim or the Me2Im in the $[Ru(bpy)_2(L)_2]^{2+}$ complexes. On the other hand, the VT NMR spectroscopic data of the 4Pic complex clearly show a slow rotation of the monodentate ligands at lower temperatures, whereas the MeIm complex does not reach the stage of slow rotation under the same conditions. Assuming the ruthenium(II)−nitrogen bonds to be similar in picoline and imidazole complexes, the six-membered ring ligand has its protons *ortho* to the coordinating nitrogen lying closer to the coordination plane than the analogous protons, H(ii) and H(iv), in the heterocyclic five-membered ring. As there are no electrostatic effects expected to influence the orientational and fluxional behaviour of the monodentate ligands in the complex *cis*-$[Ru(bpy)_2(L)_2](PF_6)_2$, the differences observed for complexes with different ligands can be attributed mainly to steric differences. For the above mentioned monodentate ligands the order of steric hindrance in these complexes is found to be:

$$\text{MeIm} < \text{4Pic} < \text{Me2Im} = \text{MeBim}$$

From the atropisomerisation study on the imidazole complexes,[15,16] it is reasonable to assume that the interconversion of the 4 rotamers of I occurs by the flipping of one picoline at a time, by 180°. As all the 4 rotamers are identical, the rate of the back and forward flipping of one picoline between two rotamers is the same. This facilitates the determination of the thermodynamic parameters, because the atropisomerisation process of **1** can now be regarded as a simple dynamic system with 2-site mutual exchange, i.e. two identical compounds interconverting into each other by the flipping of one picoline ligand. Using the temperatures (T_c and the rate constants (k_c) determined at the coalescence points of the H(*ortho*) signals (235 K, 124 s^{-1}) and the H(*meta*) signals (225 K, 60 s^{-1}), from the Eyring equation,[18] the consecutively determined free energy of activation $\Delta G^{\#}$ for the picoline rotation in I is 48 kJ·mol^{-1}, the free enthalpy of activation, $\Delta H^{\#}$, is 30 kJ·mol^{-1}, and the free entropy of activation, $\Delta S^{\#}$, is −75 J·K^{-1}·mol^{-1}. The Arrhenius activation energy E_A is found to be 32 kJ mol^{-1}.

Conclusion

The *cis*-$[Ru(bpy)_2Cl_2]$ complex has been investigated for its binding properties to DNA[13,19] and DNA model bases[20] and appears to be a borderline complex with respect to monofunctional or bifunctional coordination to DNA purines. The restricted rotational behaviour of lopsided methylimidazole ligands in *cis*-$[Ru(bpy)_2(L)_2](PF_6)_2$ has confirmed the steric hindrance of the bidentate ligands with

incoming N-heterocycles.[15,16] In the present study the *cis*-$[Ru(bpy)_2(4Pic)_2](PF_6)_2$ complex is shown to be a relatively simple, but very interesting system in the investigation of the fluxional behaviour of heterocyclic monodentate ligands on octahedral complexes. The differences in fluxional behaviour between the heterocyclic six-membered ring 4Pic and the five-membered ring MeIm ligands as observed with VT NMR spectroscopy in the complexes *cis*-$[Ru(bpy)_2(L)_2](PF_6)_2$ emphasise that the coordinative behaviour of heterocyclic ligands, on six-coordinated complexes like ruthenium is influenced by small differences in steric properties. In addition, the high symmetry complex **1** has allowed for relatively easy determination of the thermodynamic parameters of the fluxional behaviour of such complexes.

Experimental Section

General Remarks: NMR: Bruker DPX 300 MHz spectrometer. For [D_6]acetone as solvent, δH = 2.06, between −90 °C and +50 °C. NOESY[21] and ROESY[22,23] spectra with mixing times of 1.0 s and 0.5 s, respectively, were obtained using the Bruker pulse programs. Hydrated $RuCl_3$ was used as received from Johnson Matthey Inc. 2,2-Bipyridine (Fluka), 4-picoline (Merck) were used without further purification. *cis*-$[Ru(bpy)_2Cl_2]\cdot 2H_2O$ was prepared according to a literature procedure.[24]

***cis*-$[Ru(bpy)_2(4Pic)_2](PF_6)_2$ (1):** Preparation was performed by a method slightly different from that reported by Henderson et al.[25] *cis*-$[Ru(bpy)_2Cl_2]\cdot 2H_2O$ (0.26 g, 0.5 mmol) and 4-picoline (0.5 g, ca 5 mmol) in 50 mL of water were refluxed for 3 hours. At room temperature the reaction mixture was filtered and to the clear red solution a concentrated aqueous solution of NH_4PF_6 (1.6 g, 10 mmol) was added. The formed precipitate was isolated by filtration and washed with water. After recrystallisation from acetone/water, complex I was obtained as an orange red microcrystalline powder that was isolated by filtration and washed with diethyl ether. Yield: 0.30 g (75%), characterisation by NMR spectroscopy and elemental analyses. Recrystallisation from acetone/water yielded red crystals suitable for X-ray diffraction study. Because of the photolability of complex I the NMR samples were stored in the dark.

X-ray Crystallographic Study: Data were collected on a Bruker SMART diffractometer equipped with graphite monochromated Mo-K_α radiation source (λ = 0.71073 Å) and a CCD detector. The frames data were processed to give structure factors using the program SAINT.[26] The crystal data and the most relevant experimental parameters used in the X-ray measurements and in the crystal structure analyses are reported in Table 2. The phase problem was solved by Direct Methods by using SIR92[27] that revealed two independent complex molecules of formula $C_{32}H_{30}F_{12}N_6P_2Ru$ and one acetone solvent molecule in the asymmetric unit. Atomic coordinates and anisotropic thermal parameters were refined by blocked full-matrix least-squares methods on F^2 using the SHELXL-97 program.[28] The hydrogen atoms were placed at their calculated positions with the geometrical constraint C−H 0.96 A and refined "riding" on their corresponding carbon atoms. The final molecular geometry was analysed with the program PARST97.[29] All calculations were carried out on the DEC Alpha 250 workstation at the Centro di Studio per la Strutturistica Diffrattometrica of C.N.R., Parma. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-143552. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44−1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Table 2. Crystallographic data and experimental details for the complex *cis*-$[Ru(bpy)_2(4Pic)_2](PF_6)_2$

Crystal data	
Empirical formula	$C_{67}H_{66}F_{24}N_{12}OP_4Ru_2$
Molecular mass	1837.335
Crystal size [mm]	0.4 × 0.3 × 0.4
Crystal system	triclinic
Space group	$P\bar{1}$
a [Å]	11.013(5)
b [Å]	14.020(5)
c [Å]	27.143(5)
α [°]	92.39(2)
β [°]	100.63(2)
γ [°]	110.10(2)
V [Å^3]	3843(2)
Z	2
d (calcd.) [gcm^{-3}]	1.588
F(000)	1848
Data collection	
T [K]	295
Index ranges	$-12 \le h \le 12$, $-15 \le k \le 15$, $-30 \le l \le 30$
Reflections collected	18829
Independent refections	10639 (R_{int} = 0.021)
Observed reflections	7910 [$F_o \ge 4\sigma(F_o)$]
Structure refinement	
Data/restraints/parameters	10639/0/1000
Weighting scheme	$w = [(\sigma^2(F_o^2) + (0.2P)^2]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness-of-fit on F^2 [a]	0.664
Final R indices (obs. data)	$R1$ = 0.0496, $wR2$ = 0.150
R indices (all data)	$R1$ = 0.0662, $wR2$ = 0.168
Largest diff. Peak and hole [e/Å^3]	0.75, −0.70

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4\ ]^{1/2}$. Goodness-of-fit = $[\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$, where n is the number of reflections and p the number of parameters.

Acknowledgments

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