cis-[$PtCl_2(NH_3)$\{2-(2-hydroxyethyl)pyridine\}] − an Analogue of the Anticancer Drug AMD473: Unusual Hydrolysis Rates and pK_a Values for the Diaqua Adduct

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The X-ray crystal structure of *cis*-[$PtCl_2(NH_3)$\{2-(2-hydroxyethyl)pyridine\}] shows that it has similar structural features to the 2-picoline analogue, the anticancer drug AMD473 (ZD0473), but undergoes aquation much more rapidly. The diaqua adduct has unusually low pK_a values which have been rationalised by molecular modelling.

Introduction

cis-[$PtCl_2(NH_3)$(2-picoline)] (AMD473) is a new anticancer drug which entered phase I clinical trials in 1997.[1,2] It is active against cisplatin-resistant cell lines, and appears to circumvent thiol-mediated resistance mechanisms whilst still maintaining the ability to form cytotoxic lesions with DNA.[2,3] In reactions of cisplatin with DNA, hydrolysis is known to be the rate-limiting step. The steric influence of 2-picoline plays an important role in decreasing the rates of hydrolysis and substitution reactions of AMD473,[4,5] and also in promoting high stereoselectivity in the formation of a GG intrastrand adduct with a 14-mer DNA duplex.[6] In order to elucidate further the role of pyridine substituents in determining the reactivity of platinum(II) picoline complexes, we have studied the hydrolysis rates of the AMD473 analogue *cis*-[$PtCl_2(NH_3)$\{2-(2-hydroxyethyl)pyridine\}] (**1**) and determined the pK_a values of its monoaqua and diaqua adducts by [^1H,^{15}N] NMR studies of complex **1** labelled with $^{15}NH_3$. The side-chain hydroxyl group introduces the potential for second coordination sphere interactions which may affect both the rate of hydrolysis and the acidity of the mono and diaqua adducts. Molecular mechanics modelling was therefore used to investigate possible hydrogen bonding between the side-chain hydroxyl group and am(m)ine or aqua ligands. The results show how both first and second coordination sphere interactions can have a major influence on the kinetic and thermodynamic properties of Pt^{II} complexes. These interactions probably also affect their anticancer activities.

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Results and Discussion

X-ray Structure

cis-[$PtCl_2(NH_3)$\{2-(2-hydroxyethyl)pyridine\}] (**1**) was synthesised using a procedure reported previously for mixed am(m)ine complexes. The crystal structure of **1** (Figure 1) shows a square-planar complex with angles close to the ideal values of 90° and 180°. The angle between the two planes defined by Cl(1)−Pt−Cl(2) and N(1)−Pt−N(2) is 4.1°. The pyridine ring of complex **1** is nearly perpendicular to the platinum plane (76°) and the α-CH_2 group is very close to the platinum atom (H_2C···Pt 3.16 Å). These structural features are similar to those of the 2-picoline complex AMD473 (103° and H_3C···Pt 3.22 Å).[4] The Pt−N1 distance (2.028 Å) is also similar to that of the 2-picoline complex (2.017 Å). No intramolecular hydrogen bonding is observed between the hydroxyl group and the two Cl ligands. The 2-hydroxyethyl group is rotated away from the Pt atom, probably due to crystal packing effects. The pattern of intermolecular hydrogen bonding observed in the crystal packing of complex **1** (Supplementary Figure S1) is different from that observed previously for AMD473. For complex **1**, the packing is dominated by intermolecular NH_3···Cl hydrogen bonding [e.g. NH(2A)···Cl(1) 2.54 Å]. Additional intermolecular hydrogen bonding involves NH_3···OH [NH(2C)···O(23) 2.20 Å], and the OH group and a Cl ligand [OH(23)···Cl(1) 2.33 Å]. The X-ray diffraction data for the diiodo analogue **6** were of much poorer quality but were sufficient to define the connectivities. The complex

is again almost square-planar, with a slight lengthening of the Pt−N bonds to 2.08 and 2.10 Å due to the stronger *trans* influence of I versus Cl. There is no significant H-bonding to the coordinated halide, and interactions involving the side-chain OH are much weaker. This demonstrates the flexibility of the side-chain and that the conformation is determined by both inter- and intramolecular interactions. An overlay of the structures of complexes **1** and **6** is shown in Supplementary Figure S2.

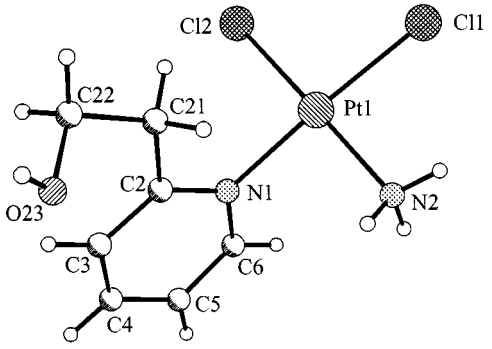
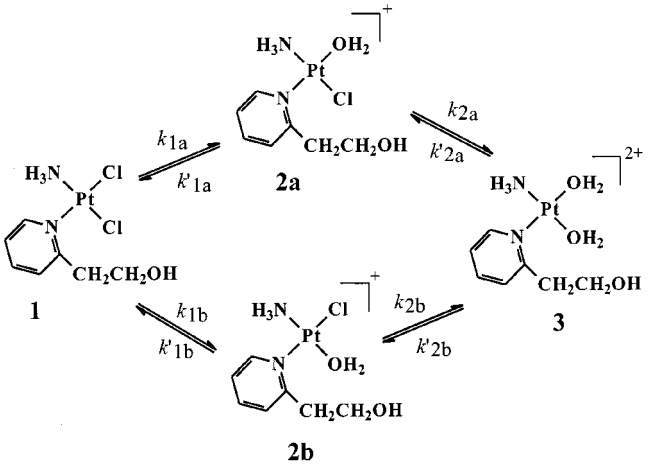


Figure 1. X-ray crystal structure of complex **1**

Hydrolysis and pK_a Values

2D [^{1}H, ^{15}N] HSQC NMR spectroscopy was used to monitor the hydrolysis of $^{15}NH_3$-labelled **1** in 0.1 M $NaClO_4$ for a period of 16 h at 298 K. Four major cross-peaks were observed in the first 2D NMR spectrum, recorded after 15 min. The assignments of the cross-peaks are based on the ^{15}N chemical shifts, which are diagnostic of the *trans* ligands,[4] and the time-dependent intensity changes of the cross-peaks. The assignments are consistent with the reaction pathway summarised in Scheme 1. The cross-peak at δ = 4.22 (^{1}H)/−65.59 (^{15}N) gradually decreased in intensity, and was assigned to the starting complex **1**. The intensity of the cross-peak at δ = 4.48/−63.30 was significantly lower than that of the cross-peak at δ = 4.40/−86.47. The ^{15}N chemical shift of the former is consistent with the assignment to the mono-aqua complex **2a** with a ^{15}N atom *trans* to Cl, while the latter peak is assignable to the monoaqua complex with the ammine trans to water (**2b**). The fourth peak at δ = 4.47/−78.07, assignable to the diaqua complex **3**, has a ^{15}N chemical shift typical of $^{15}NH_3$ *trans* to O. These shifts are similar to those observed for the 2-picoline complex AMD473.[4]

Two minor additional cross-peaks at δ = 4.34/−68.70 (complex **4**, NH_3 *trans* to N or Cl) and δ = 4.65/−82.60 (complex **5**, NH_3 *trans* to O) were present during the later stages of the aquation reaction. However, they disappeared when the pH of the solution was lowered and were therefore assigned to hydroxy-bridged species. These species were ignored in the kinetic calculations. The possibility of the formation of species containing a chelate ring by deprotonation of the hydroxyethyl side-chain and ring closure of complex **2b** was considered. Such a chelated complex would, however, contain high levels of steric strain on account of the severe steric clash between the pyridine *ortho* protons and the protons of the *cis* ammonia ligand.



Scheme 1

The time-dependence of the concentrations of species detected during hydrolysis of complex **1** (as determined by integration of NMR cross-peaks) is shown in Figure 2. Remarkably, the cross-peak for the diaqua adduct was already intense after 15 min, and the shape of the signal was very distorted in the early stages of the hydrolysis due to the lowering of pH which accompanied the hydrolysis. The percentages of the species present after ca. 16 h at 298 K were **1**: 26.4%, **2a**: 15.5%, **2b**: 30.1%, **3**:23.1%, **4**:4.6% and **5**:0.3%. The diaqua adduct is formed much faster than for the analogous 2-picoline complex. For the latter it appears only after 2.5 h even at the higher temperature of 310 K, and less than half as much is formed after 16 h.[4]

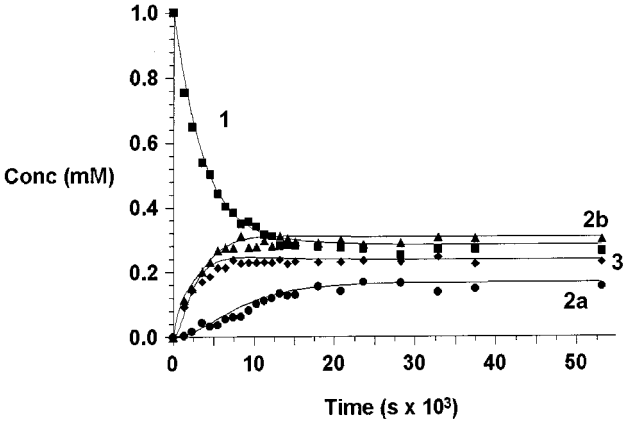


Figure 2. Dependence of the concentrations of complex **1** and its hydrolysis products on time as determined by NMR spectroscopy; labels: complex **1** (■), monoaqua complexes **2a** (•) and **2b** (▲), and diaqua complex **3** (◆); the curves represent the calculated best fits based on the rate constants given in Table 2 (see Scheme 1)

The assignments of the peaks for the mono- and diaqua complexes were further confirmed by pH titrations (Figure 3). As expected, the ^{1}H and ^{15}N chemical shift changes during the pH titration are larger for an ammine ligand

trans to an aqua ligand than when *trans* to a chloride ligand. The pK_a values of the mono- and diaqua complexes obtained by fitting the titration curves are listed in Table 1 and compared with those for the analogous 2-picoline and 3-picoline complexes, and with cisplatin.

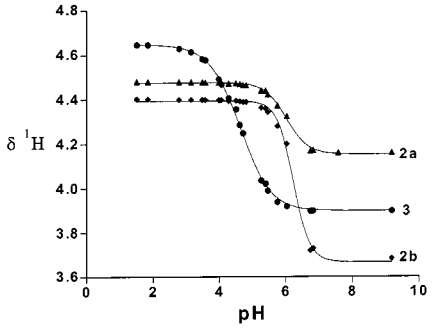


Figure 3. Dependence of the ^{1}H NMR chemical shifts of the NH_3 ligand in the monoaqua complexes **2a** and **2b** and diaqua complex **3** on pH; the curves represent best fits based on the pK_a values listed in Table 1

The rate of aquation for the chloride ligand *cis* to the pyridine ligand is much faster for complex **1** than for the 2-picoline complex AMD473 (8 × even at a temperature 12 K lower: k_{1b}, Scheme 1, Table 2). Since the X-ray crystal structures suggest that the steric effects of the pyridine side-chains are similar in the ground states of complex **1** and the 2-picoline analogue, the faster hydrolysis must arise from a lowering of the energy of the five-coordinate transition state. This may arise from H-bonding between the 2-hydroxyethyl side-chain and an incoming water ligand. The slower rate of aquation for the Cl ligand *trans* to the pyridine ligand in complex **1** in the first step of the aquation reaction (k_{1a}, Scheme 1, Table 2) is slower than for the ammine, 2-picoline or 3-picoline analogues in line with the basicities of the *trans* ligand, for which the pK_a values are in the order: NH_3 (9.29)[7] > 2-picoline (6.1), 3-picoline (6.0) > 2-(2-hydroxyethyl)pyridine (4.52).[8]

The pK_a values of the two monoaqua species of complex **1** (6.01, 6.23) are similar to those of the 2- and 3-picoline complexes (Table 1). However, the pK_a values for the diaqua adduct of complex **1** (3.90, 4.78) are significantly lower than those of the 2- and 3-picoline analogue complexes. It seems likely that a cooperative interaction between the hydroxyethyl side-chain and the H_2O/OH ligands in the diaqua complex is involved since the pK_a values for the monoaqua complexes are normal.

Molecular Modelling

The potential for hydrogen-bonding between the hydroxyl side-chain and am(m)ine or aqua ligands and its possible influence on the deprotonation of the aqua ligands was investigated by molecular mechanics modelling. A view of a molecular model of *cis*-[$Pt(NH_3)${2-(2-hydroxyethyl)pyridine}$(H_2O)_2$]·H_2O is shown in Figure 4A. The planar picoline ligand adopts an orientation perpendicular to the coordination plane. The first methylene of the hydroxyethyl side chain is necessarily disposed toward the Pt atom, but the remainder of this chain is free to adopt orientations that map out an arc lying above the coordination plane. At the two extremes of this arc, close contacts with the ligands *cis* to the picoline ligand occur and, depending on the orientation of the hydroxyl group, this contact can take the form of a hydrogen bond. The hydroxyl group can act as a hydrogen bond acceptor or hydrogen bond donor, and in the latter role would stabilise a hydroxo

Table 1. Values of pK_a for the mono- and diaqua adducts of *cis*-[$PtCl_2(NH_3)${2-(2-hydroxyethyl)pyridine}] (**1**), *cis*-[$PtCl_2(NH_3)$(2-picoline)], *cis*-[$PtCl_2(NH_3)$(3-picoline)] and cisplatin[4,23]

Adduct	**1**	*cis*-[$PtCl_2(NH_3)$(2-picoline)]	*cis*-[$PtCl_2(NH_3)$(3-picoline)]	cisplatin
Monoaqua	6.01[a]	6.13[a]	5.98[a]	6.41
Monoaqua[b]	6.23[b]	6.49[b]	6.26[b]	6.41
Diaqua	3.90, 4.78[c]	5.22, 7.16	5.07, 6.94	5.37, 7.21

[a] H_2O *trans* to picoline ligand. [b] H_2O *trans* to NH_3 ligand. [c] Average of values obtained from fits to ^{1}H NMR spectroscopic data (3.89, 4.79) and ^{15}N NMR spectroscopic data (3.91, 4.76).

Table 2. Rate constants determined for the hydrolysis of platinum complexes at 298 K (I = 0.1 M), unless otherwise stated (see Scheme 1); the errors represent one standard deviation

Complex	Rate constant (x 10^{-6} s^{-1}) (Anation rate constants × 10^{-3} M^{-1} s^{-1})[a]			
Complex **1**	k_{1a} 8.6 ± 4.5 (k'_{1a} 55.7 ± 50.3)	k_{1b} 167.9 ± 6.1 (k'_{1b} 144.1 ± 27.5)	k_{2a} 89.8 ± 58.3 (k'_{2a} 95.9 ± 26.8)	k_{2b} 737.9 ± 120.4 (k'_{2b} 95.5 ± 17.4)
AMD473[b]	k_{1a} 31.9 ± 1.5	k_{1b} 22.1 ± 1.4	k_{2a} 73.0 ± 14.0	k_{2b} 3.5 ± 2.5
3-picoline[b]	k_{1a} 44.7 ± 1.9	k_{1b} 103.0 ± 4.0	k_{2a} 35.0 ± 1.7	k_{2b} 78.0 ± 60.0
Cisplatin[c]	k_{1a} 51.8 ($k1$)	-	-	-

[a] Obtained from best fits to the curves shown in Figure 2 (see Scheme 1). The anation rates are subject to large errors because the reverse reactions are relatively fast. [b] Ref.[4] 310 K. [c] Ref.[24]

ligand in the *cis* position. Thus, it has the potential to promote deprotonation of the *cis* aqua ligand and contribute to the unusually low pK_a value. No stable orientation of the hydroxyethyl side chain resulted in a close contact with the ligand lying *trans* to the picoline ligand, primarily because of the unfavourably short contacts between the side-chain and the Pt atom that result from any disposition toward the *trans* ligand. Therefore an alternative explanation for its low pK_a was sought. A water molecule, added to the second coordination sphere close to the coordination plane and in a position to form hydrogen bonds with both aqua ligands, moved away from this plane toward the hydroxyethyl side chain on energy minimisation. In the final model (Figure 4B), this water molecule acts as a hydrogen bond acceptor to the aqua ligand *cis* to the picoline ligand and a hydrogen bond donor to both the hydroxyethyl group and the aqua ligand *trans* to the picoline. This is but one of many arrangements that might be considered, but it shows that the 2-hydroxyethyl side chain can be viewed as providing an environment conducive to the close association of a water molecule with the *cis*-[Pt{2-(2-hydroxyethyl)-pyridine}$(NH_3)(OH_2)_2]^{2+}$ complex. The Pt···OH_2 interaction is long (3.33 Å) but may provide an additional electrostatic contribution to bonding, as previously described for other Pt^{II} ammine complexes.[9,10] Hydrogen bonding between the Pt and a water molecule would be expected to stabilise the hydroxo form of the aqua ligands. In addition, the hydrophilic environment created by the 2-hydroxyethyl side chain would promote deprotonation of the aqua ligands and so contribute to their unusually low pK_a values.

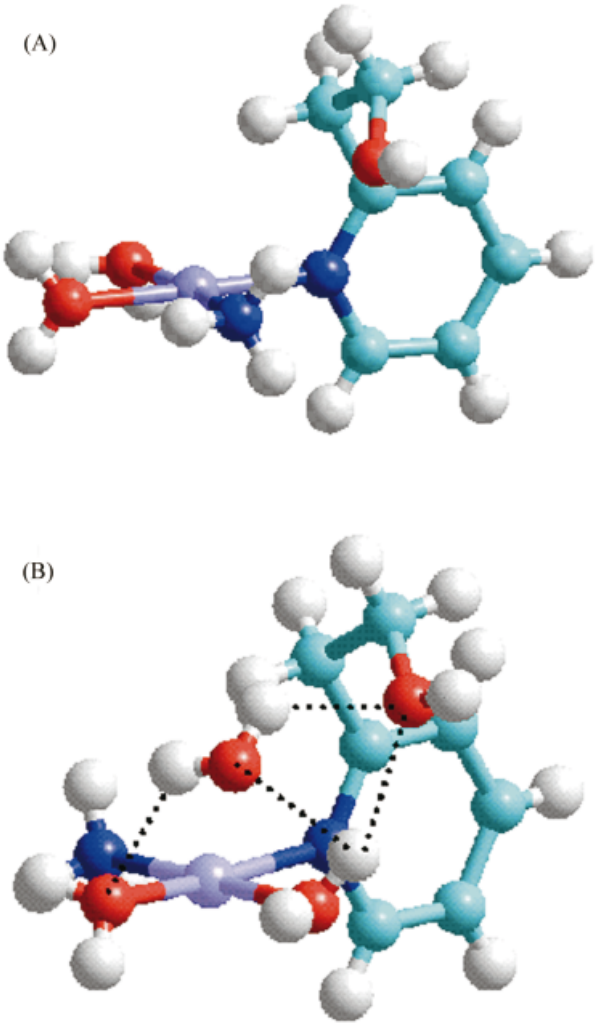


Figure 4. (A) A ball and stick view of a molecular model of *cis*-[Pt(NH_3)\{2-(2-hydroxyethyl)pyridine\}$(OH_2)_2]^{2+}$; colour code: H (white), C (cyan), O (red), Pt (dark blue), N (blue); (B) energy-minimised model of [Pt(NH_3)\{2-(2-hydroxyethyl)-pyridine\}$(OH_2)_2]^{2+}\cdot H_2O$, showing that the water molecule acts as a hydrogen bond acceptor to the aqua ligand *cis* to the picoline ligand and a hydrogen bond donor to both the hydroxyethyl group and the aqua ligand *trans* to the picoline ligand; colour code: H (white), C (green), O (red), Pt (light blue), N (dark blue)

In conclusion, complex **1** is an interesting new analogue of the anticancer drug AMD473, and it will now be interesting to investigate the effects of the rapid hydrolysis of complex **1** and low pK_a values of the diaqua adduct on its biological activity in comparison with AMD473.

Experimental Section

Materials and Preparations: 2-(2-Hydroxyethyl)pyridine was purchased from Aldrich. *cis*-[$PtCl_2(^{15}NH_3)$\{2-(2-hydroxyethyl)-pyridine\}] (**1**) and the iodide analogue **6** were prepared by a similar procedure to that described in the literature for natural abundance, mixed-ligand am(m)ine Pt^{II} complexes.[11] Crystals suitable for X-ray diffraction were obtained by recrystallisation from water, in the case of **1** by very slow evaporation of solvent in the presence of 0.5 M NaCl.

pH Measurements: These were obtained on a Corning 145 pH meter equipped with an Aldrich micro combination electrode calibrated with Aldrich buffer solutions of pH 4, 7 and 10. The values of pH were adjusted with 1 M $HClO_4$ or NaOH as appropriate.

NMR Spectroscopy: NMR spectra were recorded on a Bruker DMX500 instrument using 5 mm tubes, as described previously.[4] The chemical shift references were sodium trimethylsilyl[D_4]propionate for ^1H, and $^{15}NH_4Cl$ in 1.5 M HCl for ^{15}N (external).

X-ray Crystallography

Crystal Data for Complex 1: $C_7H_{12}Cl_2N_2OPt$, M = 406.18, monoclinic, space group $P2_1/c$; a = 9.608(5), b = 10.722.(6), c = 10.608(5) Å, β = 100.72(5)°, V = 1073.8(9) $Å^3$, Z = 4, ρ_c = 2.512 g cm^{-3}, $F(000)$ = 752, μ(Mo-K_α) = 13.53 mm^{-1}, yellow block 0.38 × 0.24 × 0.12 mm^3. Data were collected to 2θ = 50° at 220 K in the manner described above. An absorption correction was applied by Gaussian integration following refinement of the crystal dimensions and face indices against a set of ψ-scans (Stoe X-SHAPE;[12] range of T: 0.364−0.737). The structure was solved by Patterson methods (DIRDIF)[13] and refined against F^2 using SHELX-97. H-atoms were treated as described above. The refinement converged to $R1$ = 2.98% [for 1552 data with $F > 4\sigma(F)$], $wR2$ = 6.36% (for all 1908 unique data), S = 1.021. The final difference map extremes were +1.39 and −1.02 $eÅ^{-3}$.

Crystal Data for Complex 6: $C_7H_{12}I_2N_2OPt$, M = 589.08, monoclinic; space group $P2_1/c$; a = 7.253(4), b = 20.702.(9), c = 8.834(5) Å, β = 113.68(4)°, V = 1213.4 $Å^3$, Z = 4, ρ_c = 3.225 g cm^{-3}, $F(000)$ = 1040, μ(Mo-K_α) = 16.62 mm^{-1}, yellow lath 0.43 × 0.18 × 0.10 mm^3. Data were collected to 2θ = 50° in ω-θ mode at 220 K

on a Stoe Stadi-4 diffractometer equipped with an Oxford Cryosystems low-temperature device. The diffraction peaks had irregular profiles and high, uneven backgrounds; perhaps for this reason, intensity versus ψ plots derived from azimuthal scans showed significantly different intensities for reflections differing in ψ by 180°. Not surprisingly, an attempt to perform an absorption correction based on these was unsuccessful, and so a DIFABS[14] correction was applied during refinement at isotropic convergence (T = 0.129−0.599). Therefore, while these data establish chemical connectivity, the displacement parameters are liable to be systematically in error as a result of the absorption correction procedure. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 (SHELX-97).[15] The OH and NH_3 groups were treated as rotating rigid groups, while other H-positions were calculated and treated using a riding model. Anisotropic displacement parameters were refined for all non-H atoms, similar restraints being applied to those of directly-bonded light atoms. The refinement converged to $R1$ = 5.96% [for 1434 data with $F > 4\sigma(F)$], $wR2$ = 14.71% (for all 2149 unique data), S = 1.045. The final difference map extremes were +2.18 and −2.12 e·Å^{-3}.

CCDC-136876 (**1**) and -136877 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Molecular Mechanics Modelling: The starting models were generated using the HyperChem program[16] and energy minimised using the MOMECPC-95[17] program and a force field based on one described elsewhere.[18−22] All models were subjected to energy minimisation using MOMECPC-95 until convergence (all shifts < 0.001 Å) was achieved.

Kinetic Measurements: Peak volumes and relative concentrations from the NMR spectra recorded during the hydrolysis of complex **1** were calculated for each time point. Appropriate differential equations were integrated numerically. A nonlinear optimisation procedure using the program SCIENTIST® (version 2.01, MicroMath Inc) was employed to determined the rate constants. The errors represent one standard deviation.

Acknowledgments

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