Structural and solution equilibrium studies on half-sandwich organorhodium complexes of (N,N) donor bidentate ligands

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Complex formation equilibrium processes of [Rh(η⁶-C₅Me₅)(H₂O)₂]²⁺ with N,N'-dimethylthelylenediamine (dm), N,N',N'-tetramethylethylenediamine (tmeda), 2-picolyamine (pin) and 1,10-phenanthroline (phen) were studied in aqueous solution by ¹H NMR spectroscopy, UV-vis spectrophotometry and pH-potentiometry. Formation and deprotonation of [Rh(η⁶-C₅Me₅)](L)(H₂O)]²⁺ complexes and exchange process of the aqua to chlorido ligand were characterized in addition to single-crystal X-ray diffraction analysis of [Rh(η⁶-C₅Me₅)](L)(CI)⁻ complexes (L = dm, tmeda and pin). Formation of complexes with significantly high stability was found except tmeda due to the sterical hindrance between the methyl groups of the chelating ligand and the areny ring resulting in an increased methyl group--ring plane torsion angle. [Rh(η⁶-C₅Me₅)](L)(H₂O)]²⁺ complexes of dm, pin, phen predominated at pH 7.4 without decomposition even in the micromolar concentration range. The complexes were characterized by relatively high chloride affinity and a strong correlation was obtained between the logK' (H₂O/CI⁻) and pK₆ of [Rh(η⁶-C₅Me₅)](L)(H₂O)]²⁺ constants for a series of (O,O), (N,O) and (N,N)-chelated complexes. For this set of 12 complexes a strong correlation between logK' (H₂O/CI⁻) values and certain crystallographic parameters was found using multiple linear regression approach. DNA binding of these complexes was also monitored and compared by ultrafiltration and fluorimetry.

Introduction

The tremendous success of Pt(II) anticancer drugs, which currently belong to the best sold and most widely used antitumor compounds, has stimulated the exploration of other effective metal-based compounds. In this context Ru-based antineoplastic metal complexes with low side effects have been developed, e.g. trans-[tetrachlorido(1H-indazole)ruthenate(III)] (KP1339/IT-139), which is currently under development against numerous human tumour types.1,2 Unfortunately, another clinically developed compound, trans-[tetrachlorido(DMSO)(imidazole)ruthenate(III)] (NAMI-A),3 failed to be successful under clinical studies. Ru(III) complexes are considered as prodrugs that are activated by reduction that provides the impetus for the development of various Ru(II) anticancer compounds. Ru is often stabilized in the +2 oxidation state by the coordination of η⁶-arene type ligands.4 Besides the numerous half-sandwich Ru(II) organometallics of the type [Ru(η⁶-arene)(X,Y)]Z²⁻, in which (X,Y) is a chelating ligand and Z is leaving co-ligand, analogous complexes of the heavier congeners Os(II) are also extensively being investigated.5,6 In addition a large number of the isoelectronic Rh(III) and Ir(III) η⁶-bound arenyl complexes were also developed showing promising in vitro anticancer activity.7 Notably, the half-sandwich organometallic compounds have attracted increasing attention not just as potential therapeutic agents, but this type of compounds offers a broad scope for the design of water-soluble catalysts for transfer hydrogenation reactions as well. In general, the type of the metal ion, the arene ring, the chelating bidentate ligand and the leaving group have a strong impact on the biological or the catalytic activity. Some structure-activity relationships have already been established,8,11 considering for instance the anticancer potency of Ru(η⁶-arene) compounds bearing ligands providing (N,N), (N,O) and (O,O) donor sets,8 or catalytic activity of Rh, Ir and Ru complexes containing 1,10-phenanthroline (phen) or its derivatives for the regeneration of NADH in the chemoenzymatic reduction of ketones.9 However, the knowledge on the aqueous solution chemistry of this type of half-sandwich organometallic compounds is still limited. Information about the stability, predominant forms at various concentrations and pH values, ratio of the active aqua and the chlorido species is strongly required for the understanding of their solution behavior. Determination of equilibrium constants

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for organometallic compounds is less abundant in the literature regarding the huge number of the synthesized structures. A panel of solution equilibrium studies of $[\text{Ru(}n^2\text{-p-cymene})(X,Y)(Z)]$ complexes is reported by Buglio et al.,\textsuperscript{12,23} while in the publications of Sadler et al. mostly $pK_a$ values were determined for $[\text{Ru}(n^2\text{-arene})(X,Y)(H_2O)]$ compounds and the hydrolysis of the chlorido complexes was also investigated in detail.\textsuperscript{14} Solution equilibrium constants for various bidentate ($O,O$)$^{15,16}$ ($O,N$)$^{16-18}$ ($O,S$)$^{19}$ and ($N,N$)$^{20}$ donor containing $\text{Rh}(n^5\text{-pentamethylcyclopentadienyl})$ ($\text{Rh}(n^5\text{-C}_5\text{Me}_5)$) coordination compounds were reported in our previous works. These results revealed that the chloride affinity of the $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(L)\text{H}_2\text{O}]]$ complexes seems to be a crucial factor, just like in case of analogous $\text{Ir}(n^2\text{-C}_5\text{Me}_5)$ and some $\text{Ru}(n^2\text{-arene})$ compounds.\textsuperscript{1,21}

While the $\text{Rh}(n^5\text{-C}_5\text{Me}_5)$ complexes of the simplest bidentate ($N,N$) donor ethylenediamine and the aromatic diimine bpy exhibited only poor anticancer activity,\textsuperscript{7} the analogous complexes of phen,\textsuperscript{7} poly(pyridyl) ligands\textsuperscript{5} and their various derivatives\textsuperscript{22} with more extended aromatic systems are reported to show remarkable cytotoxic properties in various human cancer cell lines. Due to the lack of solution equilibrium data on the latter complexes herein we investigate $\text{Rh}(n^5\text{-C}_5\text{Me}_5)$ complex of phen in addition to methylated derivatives of ethylenediamine. 2-picolylamine was also involved as a representative of a mixed ($N,N$) donor ligand containing an aliphatic amine and an aromatic imine (Chart 1). The main aim of our study is to reveal correlations between complex architectures and thermodynamic data regarding their solution behavior.

## Results and discussion

### Synthesis and X-ray structures of the organometallic rhodium(III) complexes

The rhodium(III) precursor $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(\mu\text{-Cl})\text{Cl}]]_2$ used for the complex preparation was synthesized according to literature.\textsuperscript{23} The synthesis of $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(\text{tmeda})\text{Cl}]]$ and $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(\text{phen})\text{Cl}]]$ has been already reported,\textsuperscript{24,25} herein the complexes of dmen, tmeda, pin and phen were obtained following the established procedure reported by Scharwitz et al.,\textsuperscript{25} however the 2-picolylamine complex was prepared without the chloride elimination step. Pure compounds as $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(L)\text{Cl}]\text{CF}_3\text{SO}_3$ ($L = \text{dmen, tmeda, phen}$) as triflate salt or $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(L)\text{Cl}]$ ($L = \text{pin}$) with chloride as counterion were isolated from a $\text{CH}_2\text{OH}/\text{CH}_2\text{Cl}_2$ solvent mixture in moderate to good yields (34-72%). The organometallic rhodium(III) complexes were characterized by means of standard analytical methods ($^1\text{H}$ NMR spectroscopy, elemental analysis and electrospray ionization mass spectrometry (ESI-MS)). Single crystals of $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(\text{dmen})\text{Cl}]]^+$ (1), $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(\text{tmeda})\text{Cl}]]^+$ (2) and $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(\text{pin})\text{Cl}]]^+$ (3) with $\text{CF}_3\text{SO}_3^-$ (dmen, tmeda) or $\text{Cl}^-$ (pin) counter anion were obtained by the slow evaporation method from a $\text{CH}_2\text{OH}/\text{H}_2\text{O}$ mixture at room temperature. The X-ray structures of the phen complex with various counter ions are well-documented in the literature.\textsuperscript{25,26} The ORTEP representations of the complexes 1-3 are depicted in Figs. 1-2 and S1. Crystallographic data are presented in Table S1, and selected bond lengths and angles are listed in Table 1. All complexes possess ‘piano stool’ configuration, whereby $\text{C}_5\text{Me}_5$ forms the seat and the chelating ($N,N$) ligand as well as the chlorido leaving group constitute the chair legs. Complexes 2-$\text{CF}_3\text{SO}_3$ and 3-$\text{Cl}$ crystallize in the space group $P \ 1 \ 2_1/2_1/2_1$, while complex 1-$\text{CF}_3\text{SO}_3$ is a representative of the space group $P2_12_12_1$. The molecular structures of the studied complexes were directly compared to each other and to that of the $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(\text{en})\text{Cl}]\text{ClO}_4$ complex determined

### Chart 1

[Chemical structures of the ligands: N,N'-dimethylethlenediamine (dmen), N,N,N',N'-tetramethylethlenediamine (tmeda), 2-picolylamine (pin) and 1,10-phenanthroline (phen) and the general formula of the prepared $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(L)\text{Cl}]]^+$ complexes.]

### Table 1

| Complex | Ligand | Counterion |
|---------|--------|------------|
| 1 | dmen | $\text{CF}_3\text{SO}_3^- |
| 2 | tmeda | $\text{CF}_3\text{SO}_3^- |
| 3 | pin | $\text{Cl}^- |

## Fig. 1

Molecular structures of the metal complex 1 (a) and 3 (b). Solvent molecules and counter ions are omitted for clarity. Displacement ellipsoids are drawn at 50% probability level.

## Fig. 2

Molecular structure of 2. Solvent molecules and counter ions are omitted for clarity. Displacement ellipsoids are drawn at 50% probability level (a). Comparison of the molecular structure of complex 2 (coloured with green) with $[\text{Rh}(n^5\text{-C}_5\text{Me}_5)(\text{en})\text{Cl}]]^+$ (coloured with red) (b).
in our former work (Table 1).\(^{20}\) Regarding the Rh-to-ring centroid distances in [Rh(η⁵-C₅Me₅)(en)Cl]ClO₄⁻ (1.763 Å), 1-CF₃SO₃ (1.778 Å) and 2-CF₂SO₃ (1.812 Å) we can conclude that it is increasing with the higher number of the methyl substituents. The bond lengths between Rh and the nitrogen donor atoms show a similar trend. However, not only these bond lengths represent considerable differences, as the methyl group–ring plane torsion angles become higher and higher in the order of the complexes of en, dmen and tmeda as well (Table 1). This observation is well-represented when the structures of [Rh(η⁵-C₅Me₅)(en)Cl] and 2 are superimposed (Fig. 2). It is clearly seen that the methyl groups of the C₅Me₅ moiety are out of the plane of the ring system in 2. Most probably the steric hindrance between the methyl groups of the arenyl ring and the tetramethylated ligand results in the elongated Rh-to-ring centroid, Rh-N distances and the bigger torsion angle (7.50°) in complex 2. Relatively long Rh-N bond lengths are also reported for the analogous [Ru(η⁵-C₅Me₅)(tmeda)Cl] and [Ir(η⁵-C₅Me₅)(tmeda)Cl] complexes, in which 8.5° and 7.0° methyl group–ring plane torsion angles are calculated respectively based on the published data.\(^{10,27}\) Therefore, our findings predict a lower solution stability of 2 compared to the complex of ethylenediamine.

It is worth mentioning that a significant difference is also observed between the N1–C–C–N2 torsion angles in the case of the various (N,N) donor ligands. Compounds bearing only aliphatic amines (en, dmen, tmeda) have torsion angle falling in the range of 53.82–56.62°, while for the rigid bpy and phen fairly low torsion angles (0.00°, 0.24° respectively) were observed. This torsion angle for the complex of 2-picolyamine (3-Cl) falls between these extremities (25.63°).

| Bond lengths (Å) | 1-CF₃SO₃ | 2-CF₂SO₃ | 3-Cl |
|------------------|---------|---------|------|
| Rh–ring centroid | 1.763   | 1.778   | 1.812|
| Rh–N1            | 2.145   | 2.158(1)| 2.234(2)| 2.142(1) |
| Rh–N2            | 2.124   | 2.143(2)| 2.184(2)| 2.114(1) |
| Rh–Cl            | 2.434   | 2.406(1)| 2.431(1)| 2.427(1) |

| Angles (°)         | N1–Rh–N2 | N1–Rh–Cl   | N2–Rh–Cl  |
|--------------------|----------|------------|-----------|
| CH₃–ring plane     | 80.23    | 80.02(6)   | 80.36(7)  | 77.47(4) |
| Torsion angles (°) | 88.09    | 92.24(4)   | 90.13(5)  | 86.66(3) |

| Proton dissociation processes of the ligands and hydrolysis of the organometallic cation |

Proton dissociation constants (pKₐ) of dmen, tmeda, pin and phen (Table 2) were determined herein by pH-potentiometry in a chloride-free medium and values are in good agreement with those reported in the literature\(^{25,31}\) when account is taken of the different ionic strengths. Notably, the tertiary diamine (tmeda) has significantly lower pKₐ values compared to the secondary (dmen) and primary diamide ethylenediamine. The pKₐ (H₂L) and pKₐ (HL⁻) of 2-picolyamine are attributed to the deprotonation of the pyridinium and the primary amine nitrogens, respectively. In the case of phen only pKₐ of HL⁻ species could be determined in the studied pH range with adequate accuracy.

The hydrolytic behavior of the aquated organometallic cation [Rh(η⁵-C₅Me₅)(H₂O)]Cl⁺ has been studied previously,\(^{28}\) and the overall stability constants were reported for the μ-hydroxydioxidinuclear rhodium(III) species ([Rh(η⁵-C₅Me₅)(μ-OH)]Cl, [Rh(η⁵-C₅Me₅)(μ-OH)]²⁺) in our former work,\(^{15,28}\) and were used for the calculations.

Complex formation equilibria of [Rh(η⁵-C₅Me₅)(H₂O)]Cl⁺ with the selected (N,N) donor ligands

The complexion between [Rh(η⁵-C₅Me₅)(H₂O)]Cl⁺ (M⁺) and the studied (N,N) bidentate ligands always follows a fairly simple scheme in aqueous solution in the absence of chloride ions (Chart S1), since only mono-ligand [Rh(η⁵-C₅Me₅)(L)(H₂O)]Cl⁺ and [Rh(η⁵-C₅Me₅)(L)(OH)]Cl⁺ complexes are formed, similarly to the case of numerous analogous half-sandwich organorhodium compounds.\(^{15,20}\) Complex formation of [Rh(η⁵-C₅Me₅)(H₂O)]Cl⁺ with the ligands containing solely aliphatic nitrogen donor atoms (dmen, tmeda) was found to be a rather slow process that hindered the use of pH-potentiometric titrations. In order to overcome this problem, individual samples were prepared by the addition of various amounts of KOH under argon, and the actual pH, the ¹H NMR and UV-vis spectra were measured only after 24 h. During this period the equilibrium could be reached assuredly based on the time-dependent measurements.

The logK (ML)\(^{30}\) constant of the dmen complex was determined from the UV-vis spectral changes in the pH range from 2.0 to 5.3 (Fig. S2). The ¹H NMR spectra recorded for the dmen complex reveal slow ligand-exchange processes on the NMR time scale (T¹H/obs. ~ 1 ms) and as a consequence the peaks belonging to the free or bound metal fragment (and ligand) could be detected separately (Fig. 3). Based on the integrated peak areas of the C₅Me₅ protons in the unbound and bound fractions a logK (ML)\(^{30}\) constant could be also calculated from data collected at pH < 7.5 (Table 2), that represents good agreement with the constant obtained spectrophotometrically. According to the ¹H NMR spectra the bound dmen ligand can be found in two types of [ML]\(^{30}\) complexes which are assumed to be isomers. The free and achiral ligand in the H₂L form has two singlet peaks of the CH₃ (3.44 ppm) and CH₃ (2.80 ppm) protons and they turn to be doublet of triplets and doublet, respectively in the metal-bound forms.
These secondary amine nitrogen atoms have three different substituents and when coordinating to Rh they become chirality centers, thus formation of four different isomers is possible. This phenomenon was also observed in the case of [Pt(dmen)[Cl]2] complexes and the (S,S) and (R,R) isomers crystallized from aqueous solution. Based on the 1H NMR spectra two isomers are formed and their ratio is ca. 1:1. The ratio of the doublets represents the ratio of the nitrogens in the different chemical environment and configuration. On the other hand the ratio of the methyl protons of the C6Me5 fragment of the two complexes is also ca. 1:1. One of the isomers is most probably the (R,S) complex that was crystallized from the solution (vide supra), while the other is assumed to be the (S,R) isomer. Otherwise the ratio cannot be 1:1.

The peaks of the CH3 protons of the coordinated ligand and the C6Me5 moiety are found at higher and at lower chemical shift (δ) values, respectively in the (R,S) isomer as compared to the other isomer, as a result of the stronger steric hindrance between the Me groups in the (R,S) isomer. An upfield shift of all peaks belonging to both [ML]1+ isomers is observed in the basic pH range due to the fast exchange process between the aquated and the mixed hydroxido [ML(OH)]1+ species. Therefore, pKₐ of the aqua isomers as microscopic constants could be determined on the basis of the pH-dependent δ values (Table 2). The spectra recorded undoubtedly reveal that neither the free organometallic ion nor the free ligand is present at pH > 5.3, which means that the dmen complexes do not suffer from decomposition at pH 7.4. The decomposition is negligible even at 1 μM concentration at this pH on the basis of the stability constants determined.

On the contrary unbound ligand and organometallic fragment are detected by 1H NMR spectroscopy in the whole pH range studied (2–11.5) in the [Rh(η5-C6Me5)(en)[H2O]]+ + tmeda (1:1) system even at 1 mM concentration (Fig. 4). Notably, only one kind of [ML]1+ complex is formed in the pH range from 4 to 10 reaching the maximum fraction (% at pH 7.0) of complexes with much lower stability in the case of tmeda as compared to dmen (or even) as it was expected on the basis of the findings of the X-ray structure analysis (vide supra).

The complex formation with the aromatic nitrogen containing ligands (pin, phen) was found to be fast, although only bound fractions of the ligands and the metal ion could be detected by 1H NMR titrations in the pH range 2–11.5 (Fig. S3 for pin complex). This is the consequence of the formation of complexes with outstandingly high solution stability. Based on the spectral changes only pKₐ [ML]1+ constants were computed (Table 2).
Thus, the stability constants for the [ML]^{2+} species were determined by ligand competition measurements using spectrophotometry. Ethylenediamine was chosen as competitor. Ligand phen or pin was added to the [Rh(η^5-C5Me5)(en)]^{3+} complex and clear UV-vis spectral changes were observed due to the stepwise displacement of the originally metal-bound ethylenediamine (Figs. S5, S4). The logK_{ML}^{2+} value for the 2-picolyamine complex (Table 2) could be calculated by deconvolution of the recorded spectra using the computer program PSEQUAD.\textsuperscript{11} However, only a lower limit for the phen complex could be estimated, as the displacement of ethylenediamine was quantitative. Representative concentration distribution curves for the [Rh(η^5-C5Me5)(H2O)]^{3+} – 2-picolyamine system were computed on the basis of the stability constants determined (Fig. S3.b). They exhibit the predominant formation of the [ML] complex up to pH 7.0. The direct comparison of the logK_{ML}^{2+} values is not adequate, since the complex formation equilibrium is superimposed by other accompanying equilibria, such as (de)protonation of the ligands and hydrolysis of the organometallic cation. As only the ligands differ in this series (the metal ion is the same), conditional stability constants (logK_{f,ML}^{2+}) were computed at pH 7.4 taking into consideration the different basicities of the ligands (Table 2). Ligands containing two aromatic nitrogen donors (phen, bpy) form the highest stability complexes, and the other ligands give the following trend: pin > en ~ dmen >> tmeda.

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**Fig. 3** $^1$H NMR spectra for the [Rh(η^5-C5Me5)(H2O)]^{3+} – dmen (1:1) system recorded at the indicated pH values with peak assignation: peaks of dmen (a); peaks of C5Me5 (b) \(c_{\text{dmen}} = c_{\text{C5Me5}} = 1 \text{ mM}; T = 25 \ ^\circ \text{C}; I = 0.20 \text{ M (KNO}_3); 10\% \text{ D}_2\text{O})\). Structures of the (R,S) isomer (c) and the (S,R) isomer (d) of [Rh(η^5-C5Me5)(dmen)(H2O)]^{3+}.

**Fig. 4** High-field region of the $^1$H NMR spectra for the [Rh(η^5-C5Me5)(H2O)]^{3+} (M^{3+}) – tmeda (1:1) system recorded at the indicated pH values \(c_{\text{tmeda}} = c_{\text{Tmeda}} = 1 \text{ mM}; T = 25 \ ^\circ \text{C}; I = 0.20 \text{ M (KNO}_3); 10\% \text{ D}_2\text{O})\) (a). Concentration distribution curves for the [Rh(η^5-C5Me5)(H2O)]^{3+} – tmeda (1:1) systems calculated on the basis of the stability constants determined \(c_{\text{tmeda}} = c_{\text{Tmeda}} = 1 \text{ mM}; T = 25 \ ^\circ \text{C}; I = 0.20 \text{ M (KNO}_3))\) (b).
The chloride-water exchange process was studied at a pH value where the formation of the [ML]$_2^{2+}$ complex is 100% (pH = 7.0-7.4). The reaction was found to be fast in all cases and takes place within a few minutes. The logK$^\circ$ (H$_2$O/Cl$^-$) constants were calculated by the deconvolution of UV-Vis spectra of the [Rh(η$^5$-C$_5$Me$_5$)Cl(L)(H$_2$O)]$^{2+}$ complexes recorded at various chloride ion concentrations. The displacement of H$_2$O by Cl$^-$ results in characteristic spectral changes in the spectra as Fig. S5 shows for the [Rh(η$^5$-C$_5$Me$_5$)(dmen)(H$_2$O)]$^{2+}$. In the case of the tmdea complex we could not determine this equilibrium constant since there is no appropriate condition at which the [Rh(η$^5$-C$_5$Me$_5$)(tmdea)(H$_2$O)]$^{2+}$ complex forms predominantly due its low solution stability (vide supra). The obtained logK$^\circ$ (H$_2$O/Cl$^-$) constants (2.1-2.9) are fairly high compared to the values of complexes formed with (O,O) bidentate ligands (e.g. deferiprone: 0.78$^{16}$, maltol: 1.17$^{25}$). The higher logK$^\circ$ (H$_2$O/Cl$^-$) constants indicate the higher chloride ion affinity of the complexes. As a consequence in the case of high logK$^\circ$ (H$_2$O/Cl$^-$), the more difficult replacement of Cl$^-$ by water or donor atoms of proteins is feasible. In addition the complexes bearing the neutral (N,N) donor ligands are positively charged either in their aquated (2+) or chlorinated (+) forms resulting in their hydrophilic character. These two factors are not advantageous to the biological activity. The complexes of ethylenediamine, 2,2′-bipyridine are not cytotoxic (IC$_{50}$ > 100 μM in human breast adenocarcinoma MCF-7 cell line$^1$), on the contrary the compound [Rh(η$^5$-C$_5$Me$_5$)(phen)(Cl)]CF$_3$SO$_3$ was found to be active (e.g. IC$_{50}$ = 4.7 μM in MCF-7 cell line$^1$). Notably, [Rh(η$^5$-C$_5$Me$_5$)(L)Cl] complexes of polypyridyl ligands such as dipyrdo-[3,2-f,2′,3′-h]quinoline(dppq) or dipyrido[3,2-a:2′,3′-c]phenazine (dppz) were reported to be similar or even more cytotoxic due to their intercalative binding into DNA.$^7$

Analysis of the logK$^\circ$ (H$_2$O/Cl$^-$) and pK$_{a}$ [ML]$_2^{2+}$ constants being available in the literature for half-sandwich [Rh(η$^5$-C$_5$Me$_5$)(XY)(H$_2$O)]$^{2+}$ complexes (where XY is a bidentate ligand, Table S2) clearly reveals the strong correlation between these values as shown in Fig. 6. The coordinated ligands in the complexes are: deferiprone$^{16}$ as (O,O) donor, 2-picolinic acid,$^{16}$ 6-methylpicolinic acid,$^{17}$ quinoline-2-carboxylic acid,$^{17}$ 3-isouquinolinocarboxylic acid,$^{17}$ 8-hydroxyquinoline,$^{18}$ 8-hydroxyquinoline-5-sulfonate$^{18}$ and 7-(1-piperidinylmethyl)-8-hydroxyquinoline$^{18}$ as (O,N) donor and en,$^{20}$ dmen, pin, bpy$^{20}$ and phen as (N,N) donor. The higher logK$^\circ$ (H$_2$O/Cl$^-$) is accompanied by a lower pK$_{a}$ [ML]$_2^{2+}$ meaning the stronger tendency for the deprotonation of the coordinated water, thus higher OH$^-$ affinity of the complex. Since both the logK$^\circ$ (H$_2$O/Cl$^-$) constants and the X-ray crystal structures of [Rh(η$^5$-C$_5$Me$_5$)(XY)(Cl)]$^{18}$ complexes of the same set of ligands listed above are reported in the literature (or determined in this work for some (N,N) donor bearing compounds), we examined their correspondence to cover a structure-property relationship. Different crystallographic parameters were involved in the analysis such as Rh--ring centroid distance, Rh-donor atom, Rh-Cl bond lengths, X-Rh-Y, X-Rh-Cl, Cl-Rh-Y angles, methyl group-ring plane torsion angle in addition to the charges of the [ML]$_2^{2+}$ complexes (Table S3). First of all we investigated which factors show a linear relationship with the logK$^\circ$ (H$_2$O/Cl$^-$) constants. Then multiple linear regression approach was performed by Microsoft Excel. The logK$^\circ$ (H$_2$O/Cl$^-$) constants were predicted as a function of the linear combination of a set of selected crystallographic
Among the various equations the following one gave the best-fitting straight line:

\[
\text{calculated } \log K'(H_2O/Cl^-) = 27.59 \times \text{distance(Rh-centroid)} - 0.23 \times \text{angle(X-Rh-Y)} - 0.23 \times \text{methyl group-ring plane torsion angle} + 0.46 \times \text{charge of [ML]} - 28.75.
\]

The calculated \( \log K'(H_2O/Cl^-) \) constants are plotted against the values determined spectrophotometrically in Fig. 7. Based on these findings we can conclude that the chloride affinity shows dependence on the Rh-centroid distance, X-Rh-Y angle and the methyl group-ring plane torsion angle. Based on this finding the \( \log K'(H_2O/Cl^-) \) for a novel \([\text{Rh} (\eta^5-C_5\text{Me}_5)(L)(Cl)]\) complex can be predicted based on the crystallographic data.

**Interaction of \([\text{Rh}(\eta^5-C_5\text{Me}_5)(L)(Cl)]\) complexes with DNA**

DNA is a classical target for metallodrugs in general and was suggested for the complex \([\text{Rh}(\eta^5-C_5\text{Me}_5)(phen)(Cl)]\) as well.\(^7\) However, other primary targets such as proteins are also considered for anticancer half-sandwich Rh and Ru complexes. In order to compare the DNA binding affinity of \([\text{Rh}(\eta^5-C_5\text{Me}_5)(phen)(Z)]\) to that of other \([\text{Rh}(\eta^5-C_5\text{Me}_5)(X)(Y)(Z)]\) complexes (\(Z = \text{Cl}^-\) or \(H_2O, \text{charged} \) emitted) ultrafiltration/UV-vis and fluorescence measurements were carried out.

The binding of \([\text{Rh}(\eta^5-C_5\text{Me}_5)]\) complexes of deferiprone, 2-picolinic acid, quinoline-2-carboxylic acid, 3-isooquinolinocarboxylic acid, 8-hydroxyquinoline, en, dmen, tmeda, pin, bpy and phen towards DNA from calf thymus was studied by ultrafiltration/UV-vis quantification with a 10 kDa cutoff membrane filter. The binding was monitored at 1:1 complex-to-nucleotides ratio, at pH 7.4 and at 37 °C.

The chloroquine concentration of the samples was 4 mM according to cell nucleus. The low molecular mass (LMM) samples were analyzed by comparing their UV-vis spectra with the corresponding reference spectra yielding the fractions of the bound (and unbound) compounds (Fig. 8). Binding of \([\text{Rh}(\eta^5-C_5\text{Me}_5)(H_2O)])\) was also involved (notably in the presence of chloride ions the aqua ligand is partly replaced by Cl\(^-\)). Based on the recorded spectra for the LMM samples it could be concluded that these complexes do not suffer from decomposition during the DNA binding since no ligand release was observed. Comparing the bound metal complex fractions significant differences are seen. The fragment \([\text{Rh}(\eta^5-C_5\text{Me}_5)(H_2O)])25\) showed the strongest binding exceeding that of the intercalating etidium bromide (EB). The \([\text{Rh}(\eta^5-C_5\text{Me}_5)]\) complex of 8-hydroxyquinoline exhibited the highest bound fraction among the studied \([\text{Rh}(\eta^5-C_5\text{Me}_5)(X)(Y)(Z)]\) compounds, while not merely \([\text{Rh}(\eta^5-C_5\text{Me}_5)(phen)(Z)]\) but \([\text{Rh}(\eta^5-C_5\text{Me}_5)(en)(Z)]\) (without ligand with aromatic ring) also shows considerable binding. The binding behavior was further investigated by spectrofluorimetry in the case of \([\text{Rh}(\eta^5-C_5\text{Me}_5)(H_2O)])\) (without ligand) and the \([\text{Rh}(\eta^5-C_5\text{Me}_5)]\) complexes of phen and ethylenediamine by the use of the fluorescent DNA probe EB. This compound has weak intrinsic fluorescence emission, but the adduct formation with DNA results in enhanced fluorescence intensity. Emission spectra were recorded for the DNA–EB system in the absence and in the presence of the metal complexes of phen and ethylenediamine, and the fraction of the unbound EB was obtained by the deconvolution of the spectra. Results are shown in Fig. 56. The free EB fraction is similar for the \([\text{Rh}(\eta^5-C_5\text{Me}_5)(H_2O)])25\) and the phen complex 4, while it is lower for the complex of ethylenediamine. However, the displacement of EB by these complexes does not mean clearly their intercalative binding mode as binding to nucleobase nitrogen of DNA was also suggested by Scharwitz et al.\(^{25}\) for the complexes of phen, bpy and ethylenediamine based on UV-vis absorption, melting temperature and viscosity measurements.
The hindrance of the EB binding might be a consequence of a structural distortion of the DNA due to the covalent (coordinative) binding of the studied Rh(η^5-C₅Me₅) complexes to the donor atoms of the macromolecule. Therefore their binding to adenosine and guanosine was also compared using ¹H NMR spectroscopy at 1:1:1 Rh: nucleoside ratio at pH 7.4 (Fig. 9).

We have found that only [Rh(η^5-C₅Me₅)(H₂O)]²⁺ binds to adenosine (28 %), while binding levels to guanosine reach 28%, 35% and 72% in the case of [Rh(η^5-C₅Me₅)(H₂O)]²⁺, [Rh(η^5-C₅Me₅)(phen)][Z] and [Rh(η^5-C₅Me₅)(en)][Z], respectively. The hampered binding of the ethylenediamine complex to adenine can be explained by the steric hindrance between the NH₂ moieties of the ligand and the nucleoside (Chart S2) as it was suggested for the analogous Ru(III)- containing RAED complexes by Sadler et al.⁸ Based on these results the binding of the studied Rh(η^5-C₅Me₅) complexes to DNA via coordination of guanosine nitrogen is also feasible.

Conclusions

Metal complexes of various (N,N) donor containing ligands (dmen, tmeda, pin, phen) formed with [Rh(η^5-C₅Me₅)(H₂O)]²⁺ organometallic cation were synthesized and characterized in solid phase and in aqueous solution.

The structures of dmen, tmeda and pin complexes were determined by single-crystal X-ray diffraction showing a pseudo-octahedral ‘piano-stool’ geometry. Solution equilibria processes were studied via a combined approach using ¹H NMR spectroscopy, UV-vis spectrophotometry and pH-potentiometry and were compared to literature data of ethylenediamine and 2,2’-bipyridine. Complex formation with ligands possessing aliphatic nitrogens (dmen, tmeda) was found to be much slower compared to 2-picolylamine and phen.

Mono complexes with a general formula of [Rh(η^5-C₅Me₅)(L)(H₂O)]²⁺ are formed with significantly high solution stability except of tmeda, and decomposition was not observed even at low micromolar concentrations at physiological pH. The obtained stability trend is: phen, bpy > pin > en~dmen >> tmeda. The low solution stability of the tmeda complex is reflected in its crystallographic data, namely longer Rh-ring centroid distance, Rh-N bond and larger methyl group–ring plane torsion angle were found as compared to [Rh(η^5-C₅Me₅)(en)(Cl)]²⁺. Deprotonation of the aqua complexes is fast, and moderate pKᵢ [ML]²⁺ values (8.4-8.6) were obtained for dmen, pin and phen indicating the formation of low fraction of mixed hydroxido species [Rh(η^5-C₅Me₅)(L)(OH)]²⁺ at pH 7.4.

Based on the determined H₂O/Cl⁻ co-ligand exchange equilibrium constants the studied complexes possess high chloride ion affinity. The clear correlation was shown between the logK’ ([H₂O/Cl⁻]) and pKᵢ [ML]²⁺ constants for a series of Rh(η^5-C₅Me₅) complexes bearing (O, O), (O,N) and (N,N) donor sets. On the other hand logK’ ([H₂O/Cl⁻]) constants could be described foremost in the literature as a linear combination of a set of crystallographic parameters, that reveals a dependence of the chloride ion affinity of the complexes on the Rh-centroid distance, X-Rh-Y angle and the methyl group-ring plane torsion angle.

DNA binding of Rh(η^5-C₅Me₅) complexes of various bidentate ligands including dmen, tmeda, pin and phen as well as [Rh(η^5-C₅Me₅)(H₂O)]²⁺ cation was monitored by ultrafiltration and ethidium bromide displacement fluorescence experiments. Significant binding to DNA for [Rh(η^5-C₅Me₅)(H₂O)]²⁺ and its complexes with 8-hydroxyquinoline, phen and ethylenediamine was detected by ultrafiltration. Competition with EB was also found for
Experimental

Chemicals

All solvents were of analytical grade and used without further purification. Dmen, en, phen, pin, tmeda, [Rh(η⁵-C₅Me₅)(μ-Cl)Cl₂], adenosine, guanosine, EB, DNA from calf thymus, KCl, KNO₃, AgNO₃, HCl, HNO₃, KOH, KH-phthalate, 4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS), K₂HPO₄, NaH₂PO₄ and Na₂HPO₄ were purchased from Sigma-Aldrich in puriss quality. Milli-Q water was used for sample preparation. The exact concentration of the ligand stock solutions together with the proton dissociation constants were determined by pH-potentiometric titrations with the use of the computer program Hyperquad2013. The aqueous [Rh(η⁵-C₅Me₅)(H₂O)₃][NO₃]₂ stock solution was obtained by dissolving exact amounts of [Rh(η⁵-C₅Me₅)(μ-Cl)Cl₂] in water followed by the removal of chloride ions by addition of equivalent amounts of AgNO₃. The exact concentration of [Rh(η⁵-C₅Me₅)(H₂O)₃]²⁺ was determined by pH-potentiometric titrations employing stability constants for [(Rh(η⁵-C₅Me₅))(μ-OH)]⁺⁻ (i = 2 or 3) complex. Solutions of adenosine and guanosine were prepared on a weight-in-volume basis in a modified phosphate buffer (20 mM, pH 7.40) which contains 4 mM KCl and the concentration of the Cl⁻ ion corresponds to that of the nucleus. Stock solution of DNA from calf thymus was dissolved in 20 mM phosphate buffer containing 4 mM KCl, pH 7.40 and it was filtered after 3 days, then the exact concentration (nucleobase concentration) and purity was estimated from its UV absorption: ε₂₆₀ nm (DNA) = 6600 M⁻¹ cm⁻¹, A₂₅₀ nm / A₂₈₀ nm ~ 1.8.

pH-Potentiometric measurements

pH-potentiometric measurements determining proton dissociation constants of ligands dmen, tmeda, phen and pin were carried out at 25.0 ± 0.1 °C in water and at a constant ionic strength of 0.20 M KNO₃. The titrations were performed with a carbonate-free KOH solution (0.20 M). The exact concentrations of HNO₃ and KOH solutions were determined by pH-potentiometric titrations. An Orion 710A pH-meter equipped with a Metrohm ‘double junction’ combined electrode (type 6.0255.100) and a Metrohm 665 Dosimat burette was used for the pH-potentiometric measurements. The volume resolution of the burette is 0.001 mL and its precision is 0.002 mL. The electrode system was calibrated to the pH = -log[H⁺] scale by means of blank titrations (strong acid vs. strong base: HNO₃ vs. KOH), as suggested by Irving et al. The average water ionization constant, pH₀w, was determined as 13.76 ± 0.01 at 25.0 °C, I = 0.20 M (KNO₃), which is in accordance to literature. The reproducibility of the titration points included in the calculations was within 0.005 pH units. The pH-potentiometric titrations were performed in the pH range between 2.0 and 11.5. The initial volume of the samples was 10.0 mL. The ligand concentration was 1.0 mM. The goodness-of-fit measured in Hyperquad2013 by sigma (σ) represents the overall goodness-of-fit derived from the sum of squared residuals (calculated-experimental titration data). The model was accepted when σ was close to one (< 1.5). The standard deviation of the log/β values of species included into the model was always lower than 0.1. Samples were degassed by bubbling purified argon through them for about 10 min prior to the measurements and the inert gas was also passed over the solutions during the titrations.

Log β values for the various hydroxo complexes [(Rh(η⁵-C₅Me₅))(μ-OH)]²⁻ (i = 2 or i = 3) were calculated based on the pH-potentiometric titration data in the absence of chloride ions and were found to be in good agreement with our previously published data. Stability constants for M₂L₂H₂ complexes cannot be determined by pH-potentiometry because of several problems. In the case of dmen, complex formation was too slow to use pH-potentiometry. Also the dissociation of the tmdea complex was slow. [Rh(η⁵-C₅Me₅)(phen)(H₂O)]²⁺ and [Rh(η⁵-C₅Me₅)(pin)(H₂O)]²⁺ were formed > 90% at the starting pH value (~2.0) as a result of high stability.

UV–Vis spectrophotometric, ¹H NMR and fluorometric measurements

A Hewlett Packard 8452A diode array spectrophotometer was used to record the UV-vis spectra in the interval 200–800 nm. The path length was 1 or 0.5 cm. Equilibrium constants (proton dissociation, stability constants and H₂O/OCl⁻ exchange constants) and the individual spectra of the species were calculated with the computer program PSEQUAD. The spectrophotometric titrations were performed in aqueous solution on samples containing the ligands with or without the organometallic cations and the concentration of the ligands was 100-200 μM. The organometallic cation was also titrated (200 μM). The metal-to-ligand ratio was 1:1 in the pH range from 2 to 11.5 at 25.0 ± 0.1 °C at an ionic strength of 0.20 M (KNO₃). Measurements for 1:1 metal-to-ligand systems were also carried out by preparing individual samples in which KNO₃ was partially or completely replaced by HNO₃ and pH values, varying in the range ca.0.7–2.0, were calculated from the strong acid content. In the case of the dmen and tmdea complexes the absorbance data were always recorded after 24 h waiting time. UV-vis spectra were used to investigate the H₂O/OCl⁻ exchange processes of complexes [Rh(η⁵-C₅Me₅)(H₂O)]²⁻ at 200 μM (dmen) or 100 μM (pin, phen) concentration and at pH 7.40 (using 20 mM phosphate buffer) as a function of chloride concentrations (0–100 mM).

¹H NMR studies were carried out on a Bruker Ultrashield 500 Plus instrument. All ¹H NMR spectra were recorded with the WATERTAGE water suppression pulse scheme using DSS internal standard. ¹H NMR spectra were recorded after 24 h waiting time. Stability constants for the complexes were calculated by the computer program PSEQUAD. Fluorescence spectra were recorded on a Hitachi-F4500 fluorimeter in 1 cm quartz cell at 25.0 ± 0.1 °C. All DNA–containing solutions were prepared in 20 mM phosphate buffer with 4 mM KCl, which mimics the chloride concentration of the nucleus. The concentration of DNA from calf thymus (as nucleobases) was 20 μM, 5 μM for ethidium bromide and the EB-to-metal ion/or metal complex ratio was varied between 1:10 and 1:50. The excitation wavelength was 510 nm and the emission was read in the range of 530-680 nm, where the absorption of the metal ion and the metal complex is negligible. All samples were incubated for 24 h.
Ultrafiltration–UV–Vis measurements

Stock solutions of the Rh(η^5-C5Me5) complexes (containing deferiprone, 2-picolinonic acid, 6-methylpicolinic acid, quinoline-2-carboxylic acid, 3-isquinolincarboxylic acid, 8-hydroxyquinoline, 8-hydroxyquinoline-5-sulfonate, 7-(1-piperidinyl)methyl)-8-hydroxyquinoline, en, bpy, dmen, pin, phen) were prepared by mixing the aqueous solutions of [Rh(η^5-C5Me5)(H2O)]15 and the ligand at 1:1 ratio (cwater = 0.50-1.00 mM) in 20 mM phosphate buffer with 4 mM KCl. This kind of in situ preparation of the complexes was proved to be efficient at the indicated conditions (and at the proper incubation time for certain compounds).15-18,20 The DNA-containing samples were prepared in phosphate buffer (20 mM) containing 4 mM KCl. These samples were incubated for 24 h at 37.0 ± 0.1 °C. In the first series the DNA from calf thymus and metal complex concentration was 100-100 μM. Eppendorf Minispin Plus centrifuge and 10 kDa membrane filters (Millipore Amicon Ultra-0.5 centrifugal filter unit) were used. Samples were centrifuged for 10 min with 10000 rpm. UV-vis spectra of LMM fraction were recorded by a Hewlett Packard 8452A diode array spectrophotometer.

Preparation of metal complexes 1-CF3SO3, 2-CF3SO3, 3-Cl and 4-CF3SO3

Two equivalents of Ag(CF3SO3)2 were added to an acetone solution (10 mL) of [Rh(η^5-C5Me5)(μ-Cl)2]2 (92.71 mg, 0.15 mmol) and stirred in the dark for 30 min. The formed AgCl precipitate was filtered off and solvent was removed under vacuum. The residue was dissolved in CH2OH/CH2Cl2 (1:1, 10 mL) and two equivalents of the bidentate ligand (0.3 mmol) were added. The reaction mixture was stirred for 2 h. After concentration to dryness, complexes 1-CF3SO3, 2-CF3SO3 and 4-CF3SO3 were isolated as orange solid.

In the case of 2-picolylamine there was no need for chloride ion abstraction. Two equivalents of pin (31 μL) was added to suspension of [Rh(η^5-C5Me5)(μ-Cl)2]2 (92.71 mg, 0.15 mmol) in dichloromethane (30 mL). The mixture was stirred for 3 h at room temperature. Subsequent solvent removal under vacuum afforded 3-Cl as orange powder. The complexes were characterized by 1H NMR spectroscopy and elemental analysis in addition to X-ray crystallography. Elemental analysis of all compounds was performed with a Perkin–Elmer 2400 CHN Elemental Analyser (Perkin-Elmer, Waltham, MA) at the Microanalytical Laboratory of the University of Vienna. ESI-MS measurements were performed using a Micromass Q-TOF Premier (Waters MS Technologies) mass spectrometer equipped with electrospray ion source (Fig. S7).

Single crystals suitable for X-ray diffraction experiment of compound 1-CF3SO3, 2-CF3SO3 and 3-Cl were grown from water/methanol solution mixture (1:1, 2.0 mL).

Chemical characterization of [Rh(η^5-C5Me5)(dmen)Cl](CF3SO3)1-CF3SO3

Yield = 76 mg (50%) Anal. calc. for C38H32ClF6N2O2RhS·0.1H2O (512.6): C, 35.15; H, 5.35; N, 5.46; S, 6.26. Found: C, 35.13; H, 5.28; N, 5.55; S, 6.25. 1H NMR (500.10 MHz, CDCl3) (two isomers): δ = 1.76 (s, C5Me5); 1.78 (s, C5Me5); 2.48-2.53 (m, CH2); 2.68-2.69 (d, 3JHH = 6 Hz, CH2); 2.76-2.77 (d, 3JHH = 5.5 Hz, CH2); 2.83-2.90 (m, CH2); 2.93-2.94 (d, 3JHH = 6 Hz, CH2); 3.45-3.55 (m, CH2); 5.64-5.73 (m, NH); 6.07-6.17 (m, NH) ppm. ESI-MS (m/z): [M–Cl–H]+ (C38H32ClF6N2RhS, calc.: 525.1146) = 525.1108, [M]+ (C38H31ClF5N2RhS+, calculated: 361.0913) = 361.1085 and [M–Cl+CF3SO3]+ (C38H31F5N2O2RhS+, calculated: 475.0745) = 475.0735.

Chemical characterization of [Rh(η^5-C5Me5)(tmeda)Cl](CF3SO3)2-CF3SO3

Yield = 72 mg (66%) Anal. calc. for C41H36ClF8N2O2RhS·0.5H2O (547.9): C, 37.27; H, 5.89; N, 5.11; S, 5.85. Found: C, 37.19; H, 5.77; N, 5.31; S, 5.79. 1H NMR (500.10 MHz, CDCl3) δ = 1.63 (s, 15 H, C5Me5); 2.62-2.68 (m, 2 H, CH2); 2.80-2.88 (m, 2 H, CH2); 2.82 (s, 6 H, CH3); 3.17 (s, 6, H, CH3) ppm. ESI-MS (m/z): [M–Cl–H]+ (C50H36ClF7N2RhS+, calculated: 353.1459) = 353.1393, [M]+ (C50H35ClF6N2RhS+, calculated: 389.1226) = 389.0992 and [M–Cl+CF3SO3]+ (C50H35ClF6N2O2RhS+, calculated: 503.1058) = 503.1016.

Chemical characterization of [Rh(η^5-C5Me5)(pin)Cl](CF3SO3), 3-Cl

Yield = 44 mg (34%) Anal. calc. for C38H32ClF6N2O2Rh·0.5H2O (426.2): C, 45.09; H, 5.68; N, 5.67. Found: C, 45.26; H, 5.68; N, 6.62. 1H NMR (500.10 MHz, CDCl3) δ = 1.65 (s, 15 H, C5Me5); 4.23-4.25 (d, 3JHH = 9 Hz, 2 H, CH2); 7.45-7.47 (d, 3JHH = 8 Hz, 1 H, CH); 7.50-7.52 (t, 3JHH = 6 Hz, 1 H, CH); 7.89-7.92 (t, 3JHH = 8 Hz, 1 H, CH); 8.59-8.61 (d, 3JHH = 5 Hz, 1 H, CH) ppm. ESI-MS (m/z): [M–Cl–H]+ (C37H31ClF5N2RhS+, calculated: 345.0833) = 345.0579 and [M]+ (C37H30ClF4N2RhS+, calculated: 381.0600) = 381.0326.

Chemical characterization of [Rh(η^5-C5Me5)(phen)Cl](CF3SO3), 4-CF3SO3

Yield = 131 mg (72%) Anal. calc. for C41H36ClF8N2O2RhS (602.9): C, 45.82; H, 3.85; N, 4.65; S, 5.32. Found: C, 45.92; H, 3.83; N, 4.50; S, 5.27. 1H NMR (500.10 MHz, DMSO-d6): δ = 1.75 (s, 15 H, C5Me5); 8.22-8.25 (dd, 3JHH = 5 Hz, 3JHH = 8 Hz, 2 H, CH); 8.34 (s, 2 H, CH), 8.97-8.99 (d, 3JHH = 9 Hz, 2 H, CH), 9.42-9.43 (d, 3JHH = 6 Hz, 2 H, CH) ppm. ESI-MS (m/z): [M–Cl–H]+ (C40H31ClF7N2RhS+, calculated: 417.0833) = 417.0721 [M]+ (C40H30ClF6N2RhS+, calculated: 453.0600) = 453.0298 and [M–Cl+CF3SO3]+ (C40H30ClF6N2O2RhS+, calculated: 567.0432) = 567.0347.

Single-crystal X-ray structures analysis

The X-ray intensity data were measured on a Bruker D8 Venture diffractometer equipped with multilayer monochromator, Mo Kα INCOCAT micro focus sealed tube and Kryoflex cooling device. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted at calculated positions and refined with a riding model. The following software was used: Bruker SAINT software package using a narrow-frame algorithm for frame integration, SADABS43 for absorption correction, OLEX242 for structure solution, refinement, molecular diagrams and graphical user-interface, Shelxtl43 for refinement and graphical user-interface SHELX-201344 for structure solution, SHELXL-201344 for refinement, Platon46 for symmetry check. The crystallographic data files for complexes 1-CF3SO3, 2-CF3SO3 and 3-Cl have been deposited with the Cambridge Crystallographic Database as CCDC 1590516, 1590517.
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