SUPPORTING INFORMATION

Oxovanadium(IV) Cyclam and Bicyclam Complexes: Potential CXCR4 Receptor Antagonists

Allison Ross, Dinesh C. Soares, Danielle Covelli, Christophe Pannecouque, Laura Budd, Anna Collins, Neil Robertson, Simon Parsons, Erik De Clercq, Pierre Kennepohl, and Peter J. Sadler

Contents

1. Antiviral testing

For experimental protocols for antiviral testing, see Pannecouque, Daelemans and De Clercq *Nat. Protocol.* **2008**, *3*, 427-434.[1]

Cyclam complexes **1** (sulfate) and **2** (chloride) were inactive against both HIV-1 (strain III_B) and HIV-2 (strain ROD).

Table S1. Anti-HIV and cytotoxicity evaluation in III_B and ROD cell cultures

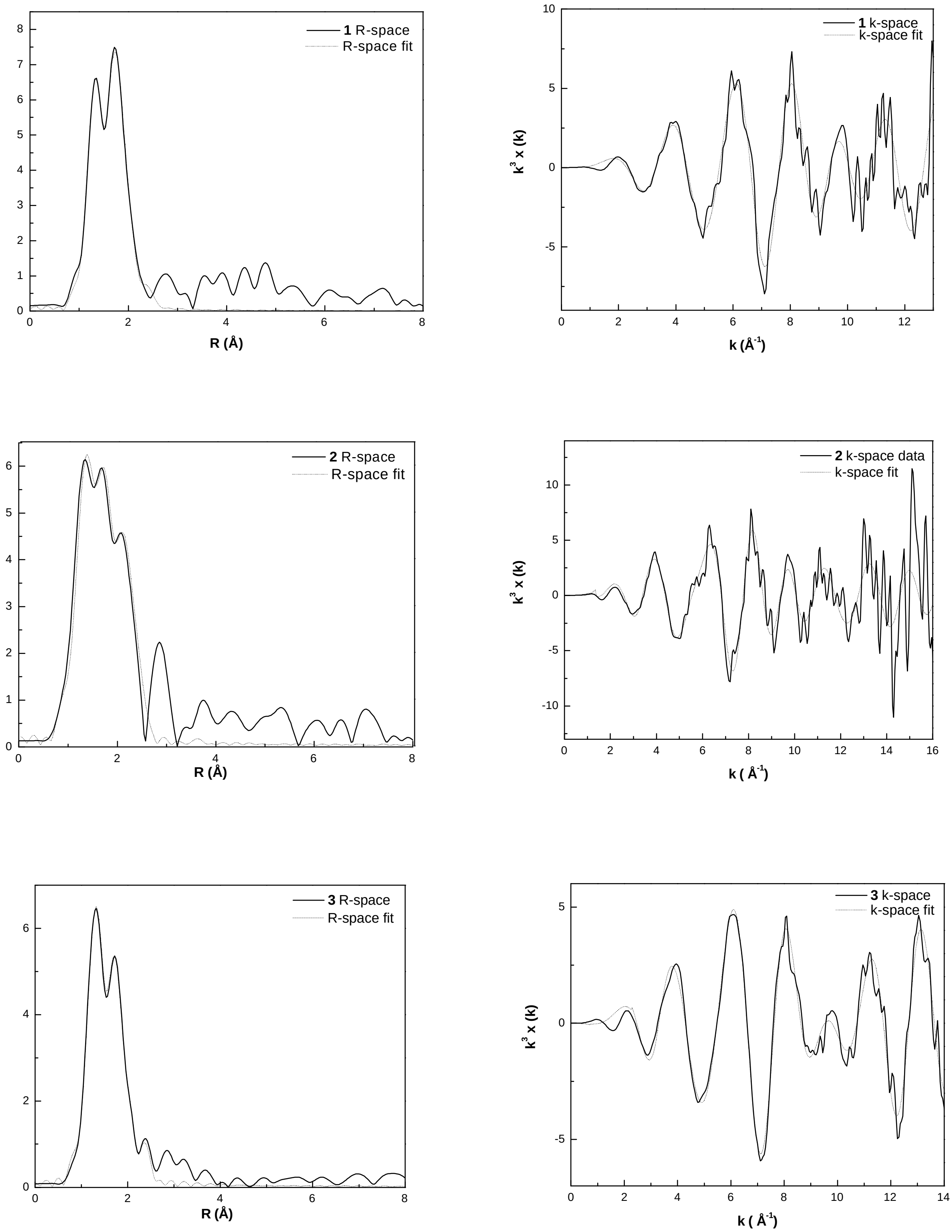
Complex	Strain	IC_{50} (µM)	CC_{50} (µM)	SI	Max Prot %	Appr	av. IC_{50} (µM)	av. CC_{50} (µM)	SI
1	III_B	> 340	> 340	x1	5	1			
		> 340	> 340	x1	4	1	> 340	> 340	x1
	ROD	> 340	> 340	x1	27	2			
		> 340	> 340	x1	24	2	> 340	> 340	x1
2	III_B	> 360	> 360	x1	4	1			
		> 360	> 360	x1	7	1	> 360	> 360	x1
	ROD	> 360	> 360	x1	14	2			
		> 360	> 360	x1	14	2	> 360	> 360	x1

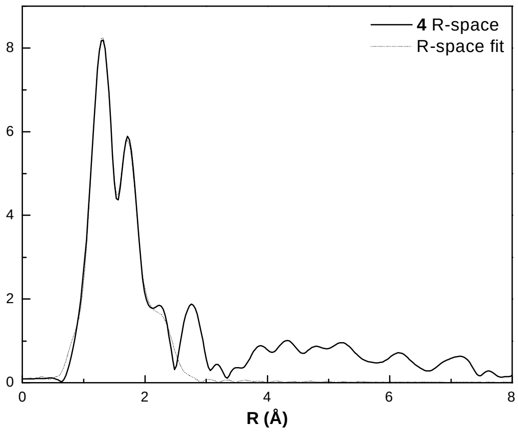
2. EXAFS data

Table S2. Statistical parameters from best R-space fits and all k-space data for complexes **1-4**.

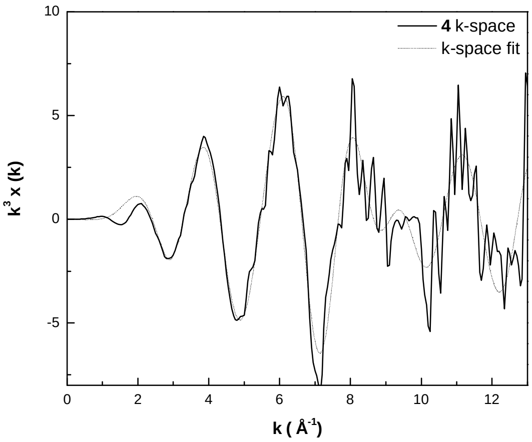
Sample	Number of Independent Variables	Chi Square	Reduced Chi Square	R-Factor
1	12	34.5	85.4	0.0027
2	12	49.2	22.4	0.0031
3	10	217.1	99.7	0.0011
4 (Fit 1)	12	23.9	59.1	0.0037
4 (Fit 2)	11	27.1	19.3	0.0042

Figure S2. EXAFS k-space data for complexes **1-4**





4 R-space
R-space fit
R (Å)
0
2
4
6
8



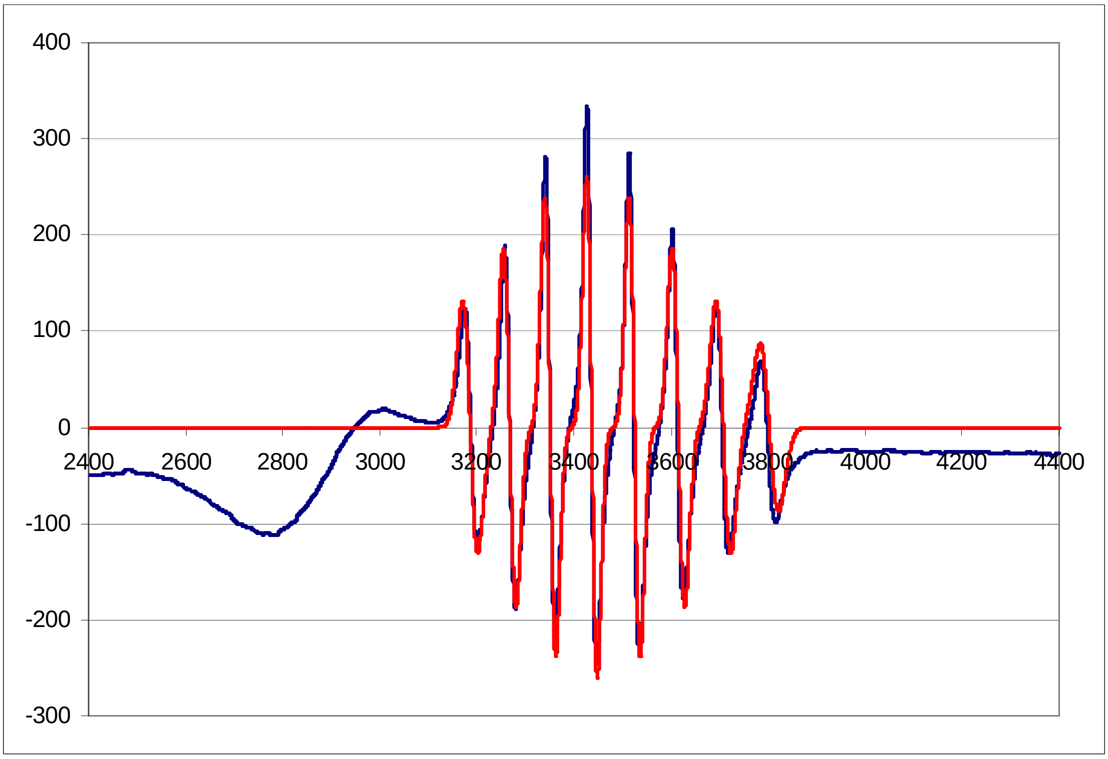
4 k-space
k-space fit
k³ x (k)
k (Å⁻¹)
10
5
0
-5
2
4
6
8
10
12

3. EPR – simulated spectra

Figure S3.

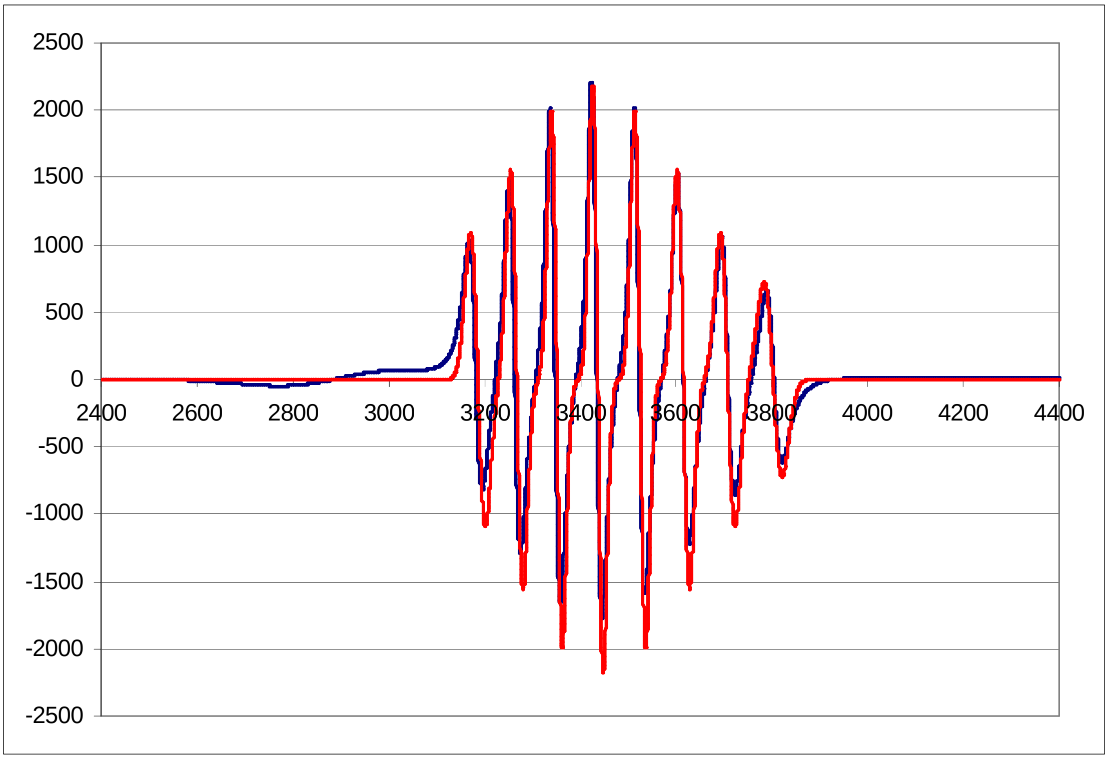
(a) $V^{IV}O$-cyclam sulfate, **1** in water at 298 K

(g = 1.972, A / G = 88)



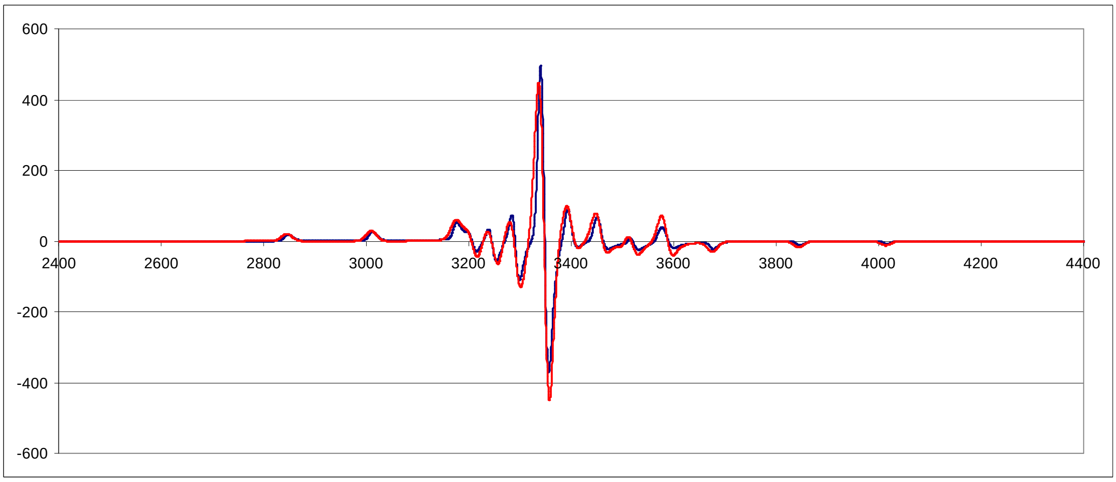
(b) $V^{IV}O$-cyclam sulfate, **1** in methanol at 298 K

(g = 1.972, A / G = 88)



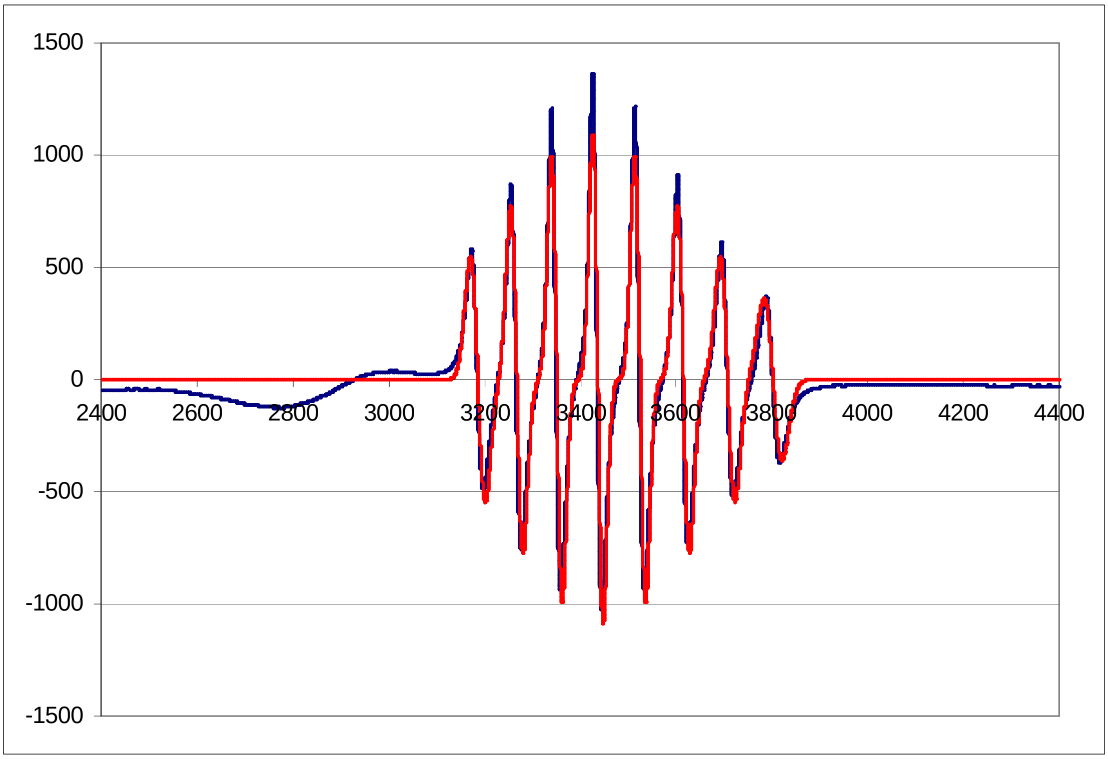
(c) $V^{IV}O$-cyclam sulfate, **1** in methanol at 77 K

($g_{x,y}$ = 1.983, A_z / G = 53; g_z = 1.968, A_z / G = 167)



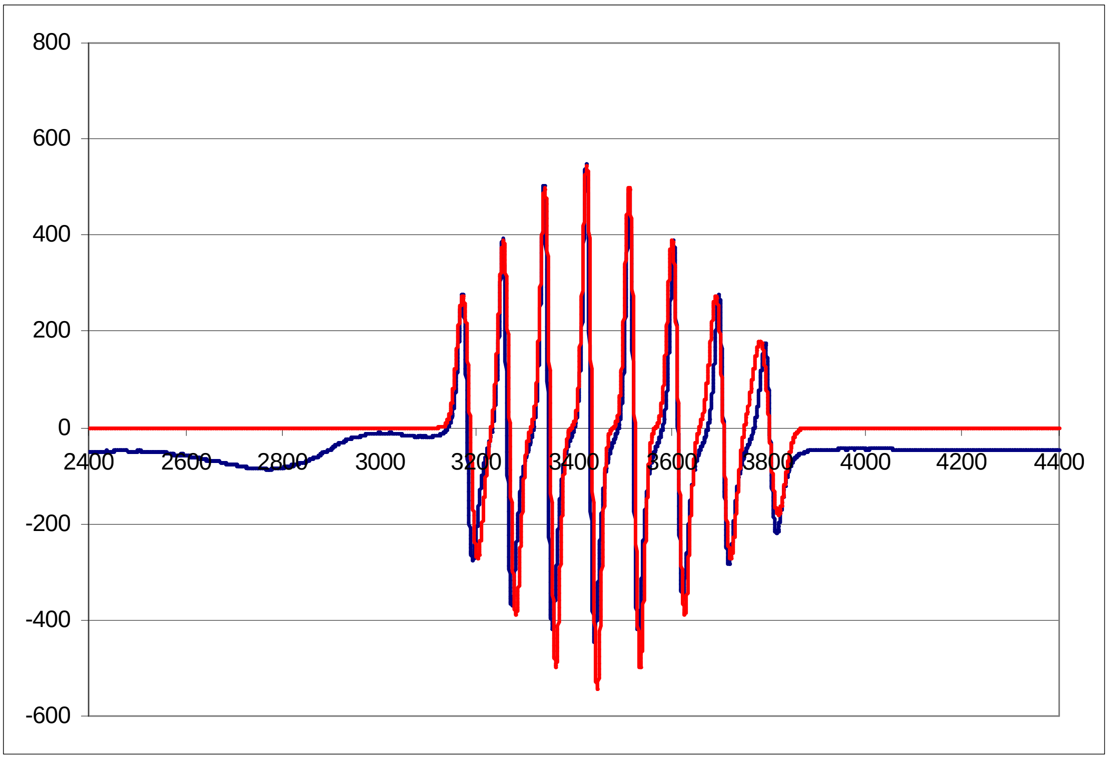
(d) $V^{IV}O$-cyclam chloride, **2** in water at 298 K

(g = 1.972, A / G = 88)



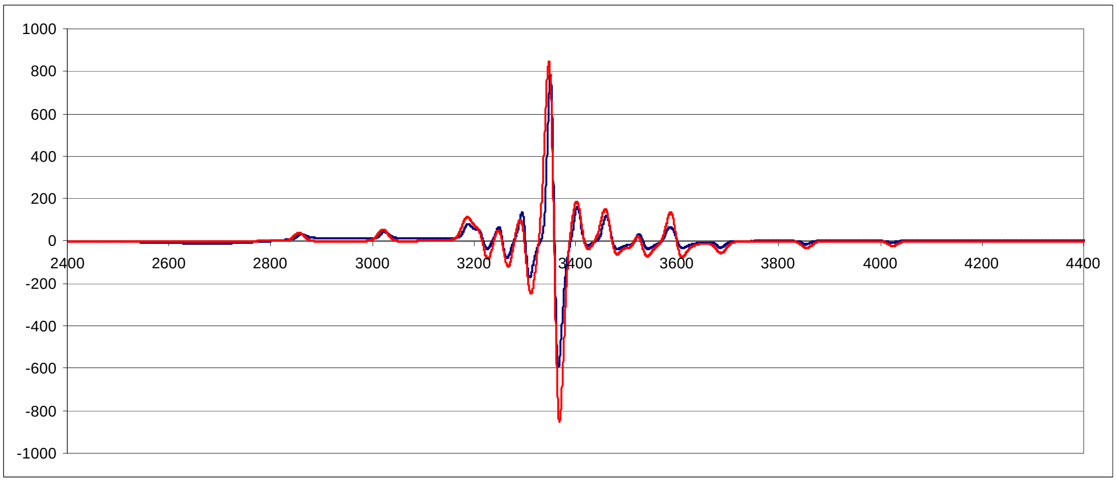
(e) $V^{IV}O$-cyclam chloride, **2** in methanol at 298 K

(g = 1.972, A / G = 88)



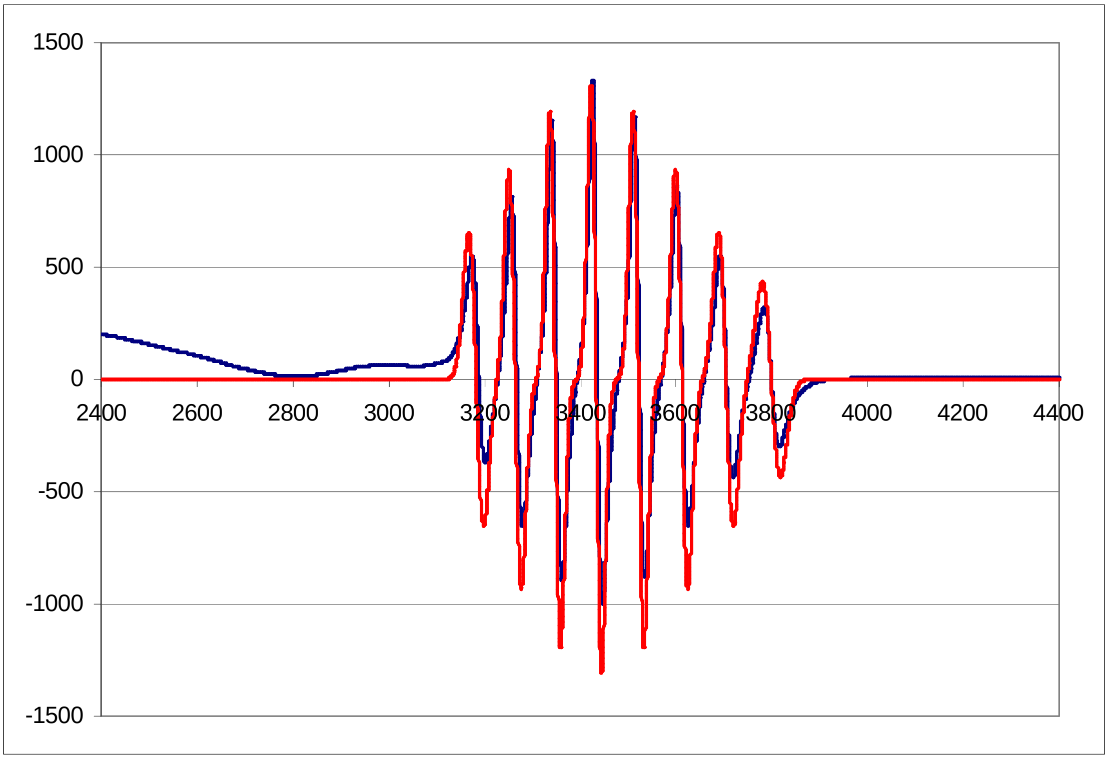
(f) $V^{IV}O$-cyclam chloride, **2** in methanol at 77 K

($g_{x,y}$ = 1.983, A_z / G = 53; g_z = 1.968, A_z / G = 167)



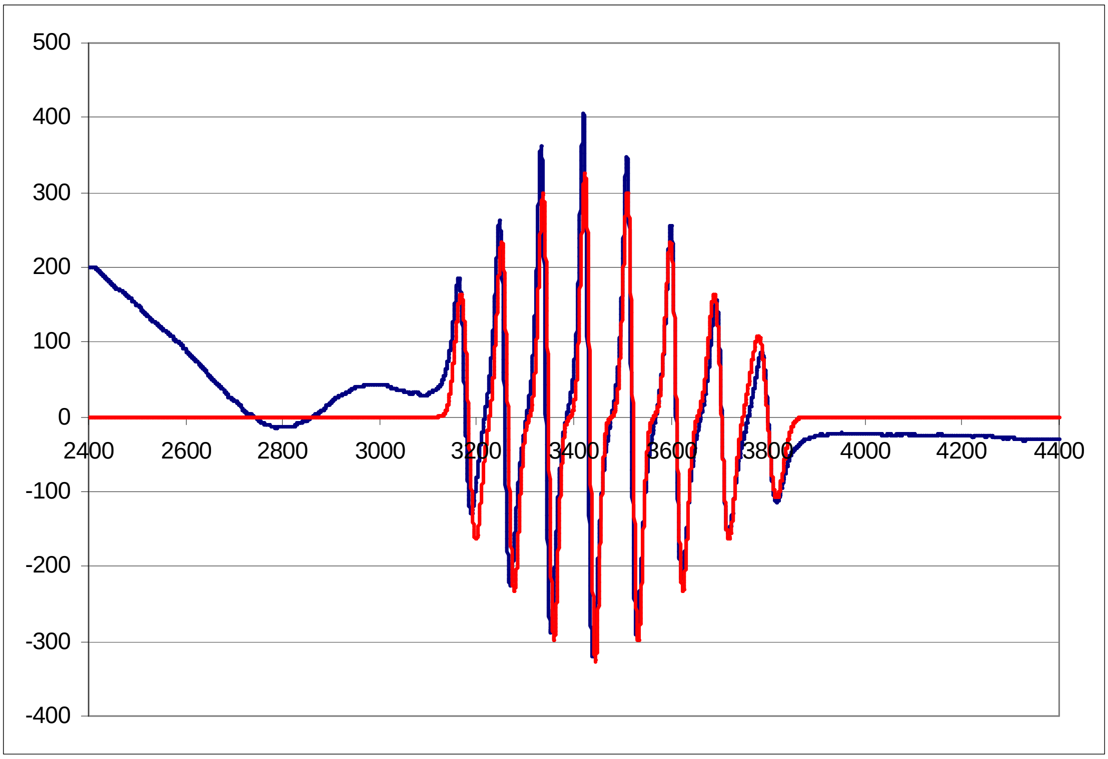
(g) $V^{IV}O$-cyclam (aqua) in water at 298 K

(g = 1.972, A / G = 88)



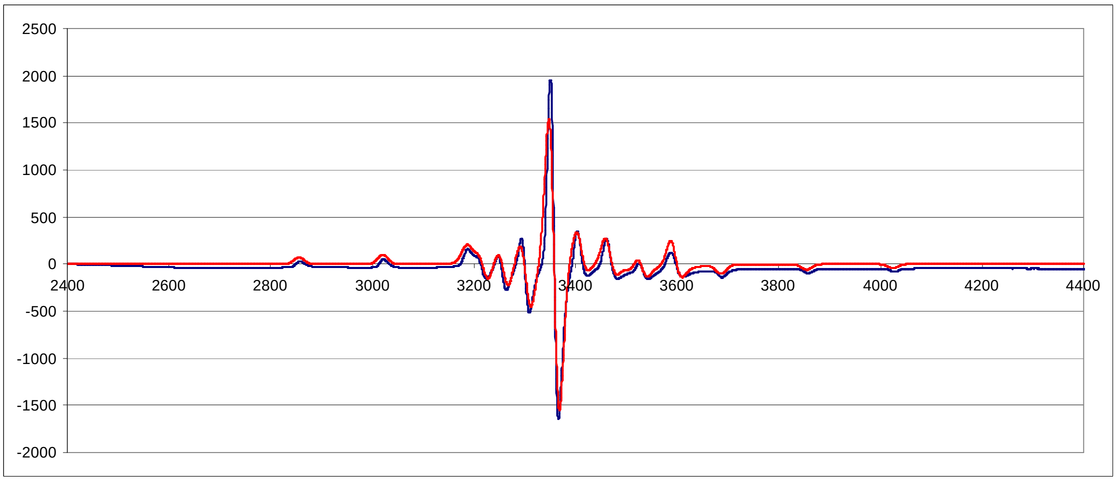
(h) $V^{IV}O$-cyclam (aqua) in methanol at 298 K

(g = 1.972, A / G = 88)



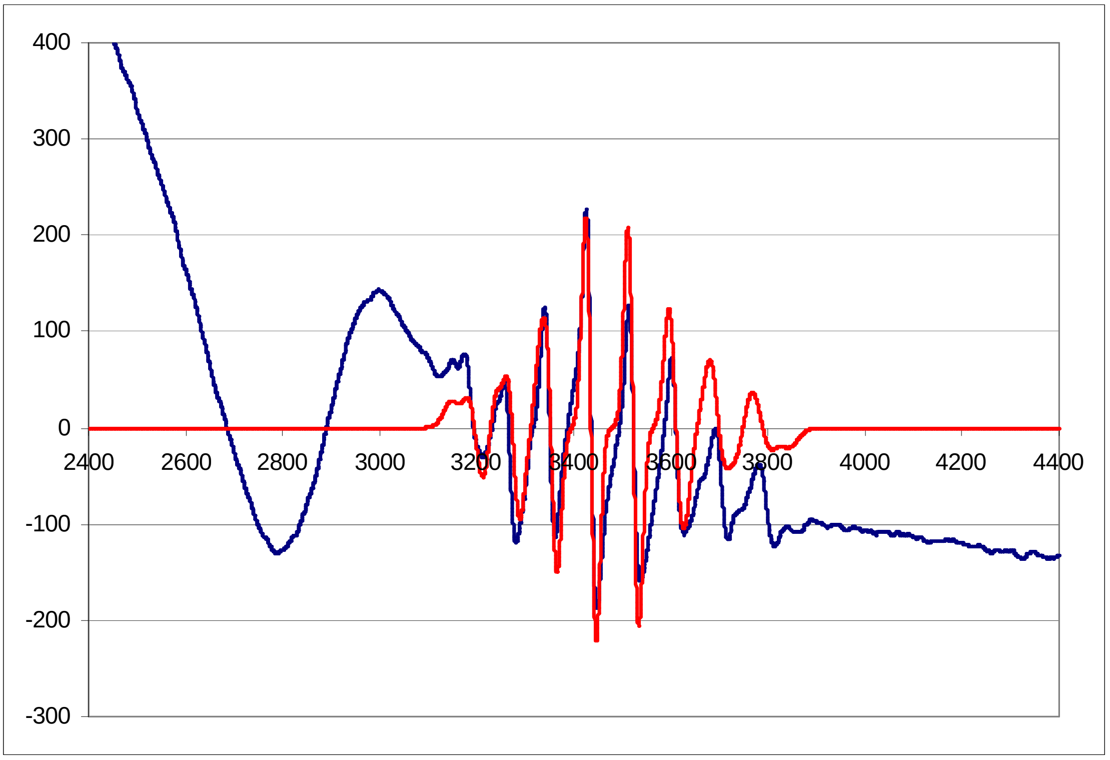
(i) $V^{IV}O$-cyclam (aqua) in methanol at 77 K

($g_{x,y}$ = 1.983, A / G = 53; g_z = 1.968, A_z / G = 167)



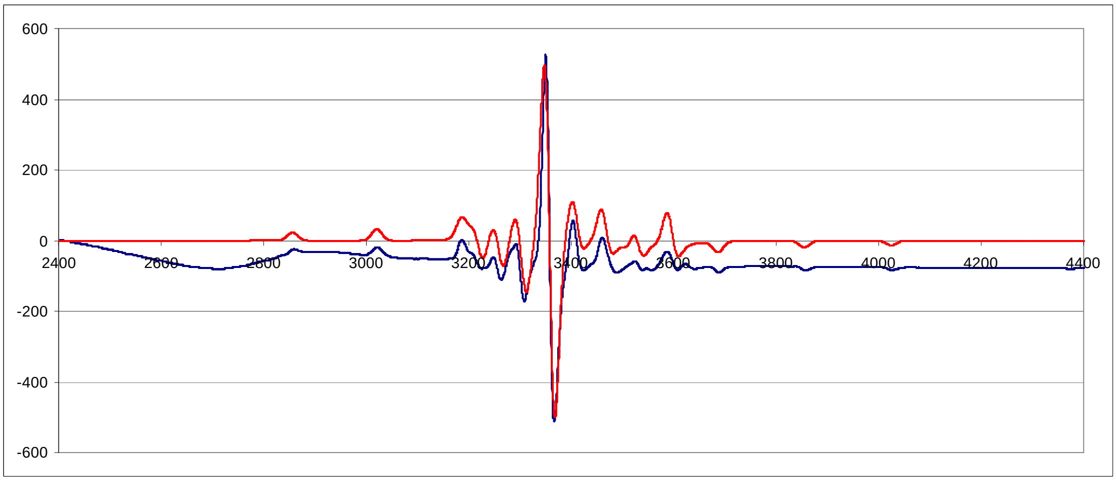
(j) [($V^{IV}O)_2$-xylylbicyclam($SO_4)_2$], **3** in water at 298 K

(g = 1.974, A / G = 84; g' = 1.972, A' / G = 95)



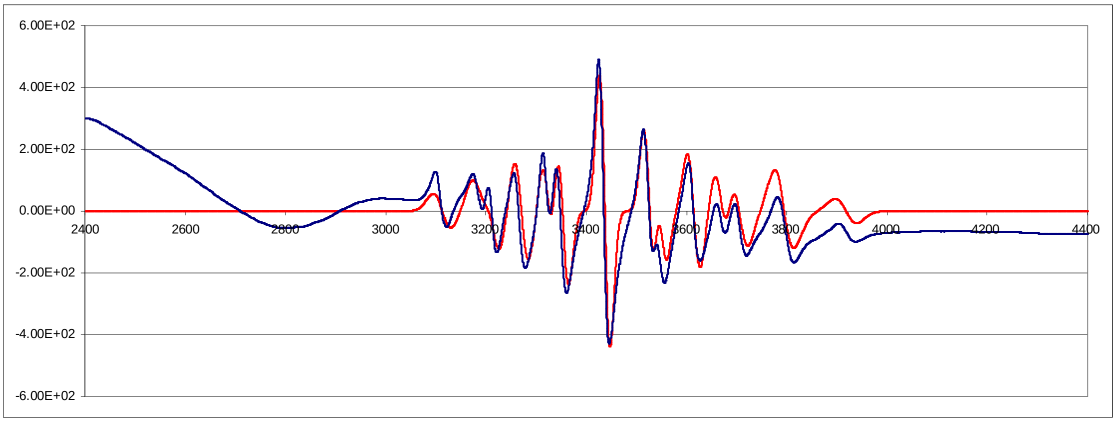
(k) [$(V^{IV}O)_2$-xylylbicyclam$(SO_4)_2$], **3** in methanol at 77 K

($g_{x,y}$ = 1.972, $A_{x,y}$ / G = 53; g_z = 1.957, A_z /G = 167)



(l) $[(V^{IV}O)_2$-xylylbicyclam$(Cl_2)]^{2+}$, **4** in water at 298 K

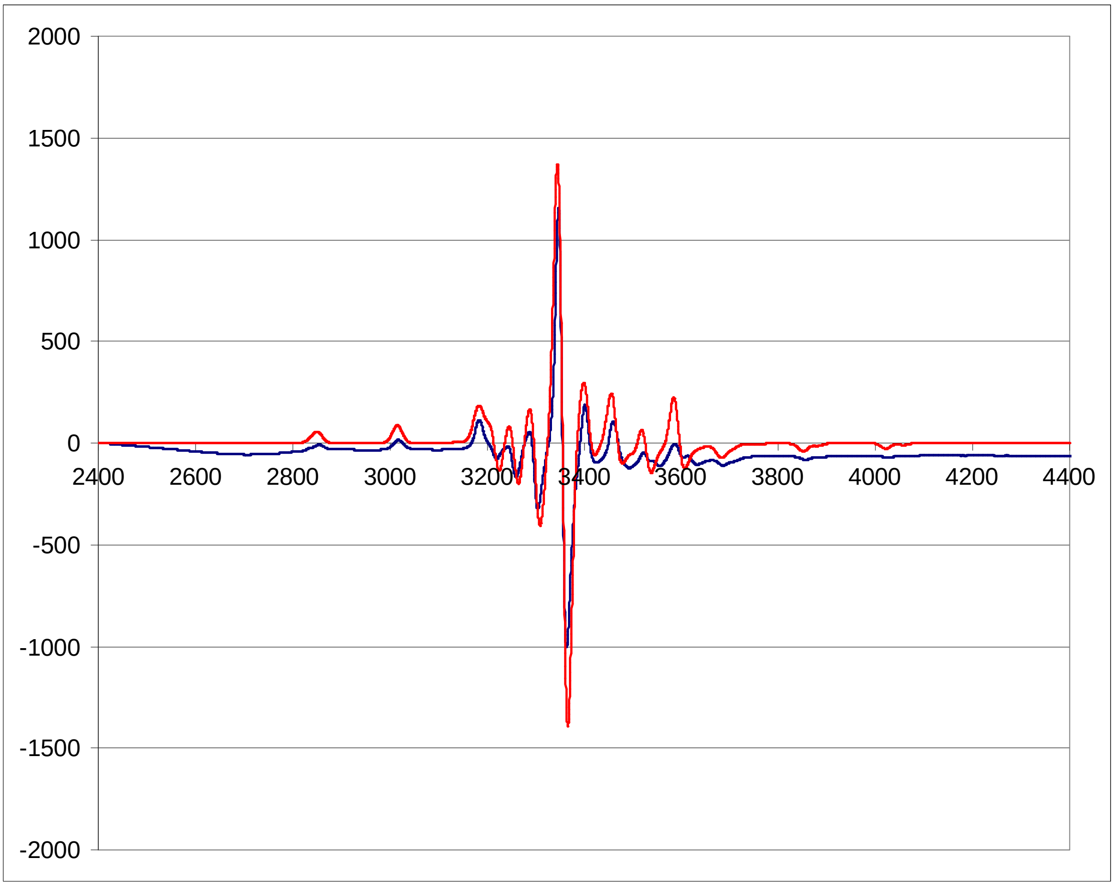
(g = 1.972, A / G = 87; g' = 1.959, A' / G = 115)



(m) $(V^{IV}O)_2$-xylylbicyclam$(Cl_2)^{2+}$, **4** in methanol at 77 K

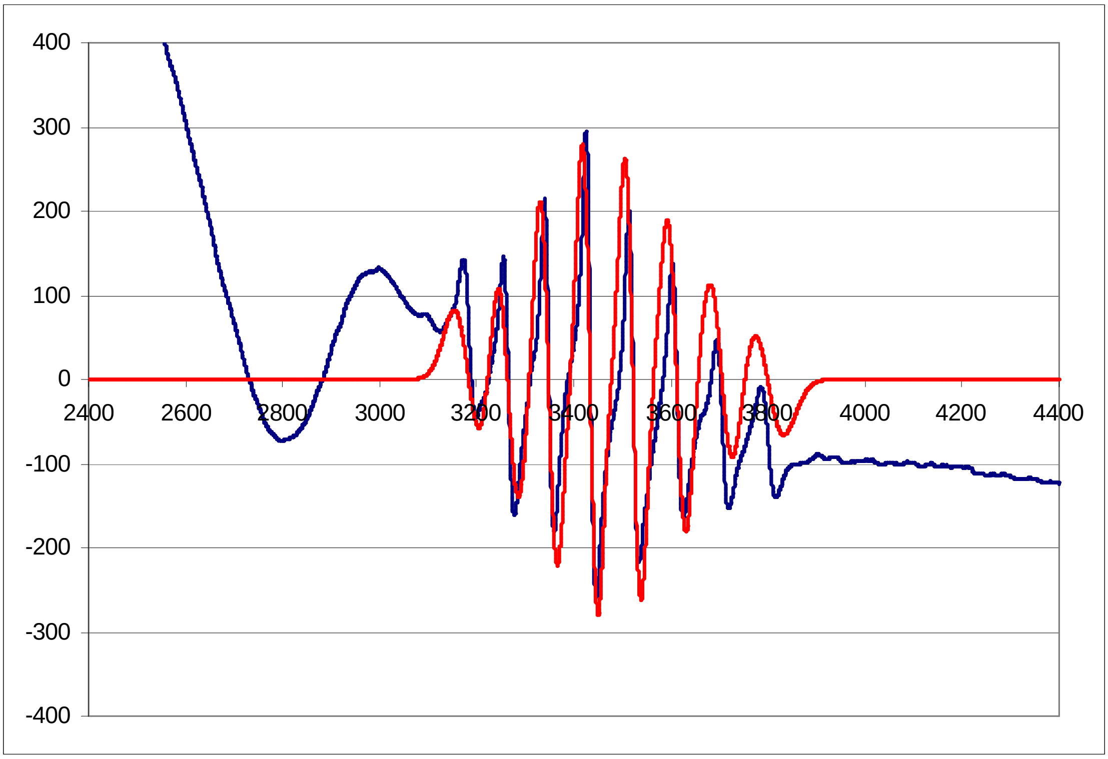
(A1: $g_{x,y}$ = 1.971, $A_{x,y}$ / G = 53; g_z = 1.957, A_z / G = 167)

(A2: $g_{x,y}$ = 1.971, $A_{x,y}$ / G = 53; g_z = 1.950, A_z / G = 174)



(n) $(V^{IV}O)_2$-xylylbicyclam(aqua) in water at 298 K

(g = 1.974, A / G = 88)



4. Synthesis procedures for solvento complexes

Aqua complexes were synthesised for EPR study to compare spectra of compounds with a solvent molecule as axial ligand *trans*- to the V=O group with those for complexes **1-4** where the axial ligand is sulfate or chloride. These were synthesised in aqueous solution by removing the chloride ligand from complexes **2** and **4** using $Ag(PF_6)$ to give the aqua complex.

Oxovanadium(IV)-1,4,8,11-tetraazacyclotetradecane·2PF$_6$

Oxovanadium(IV) cyclam dichloride **2** (250 mg, 0.74 mmol) was dissolved in 15 mL distilled water and stirred at room temperature. Silver hexafluorophosphate (374.18 mg, 1.48 mmol, 2 mol. equiv.) was added and an instant precipitate formed in the solution. The mixture was stirred at room temperature for 1 h and separated using centrifugal force (4000 rpm, 30 min). The solvent was removed by freeze-drying to give a crystalline green powder (156.74 mg, 0.59 mmol, 80%). Anal. Calc. for $C_{10}H_{26}N_4VO_2{\cdot}2PF_6{\cdot}AgPF_6{\cdot}CH_3OH$ %C, 15.36; %H, 3.52; %N, 6.51. Found %C, 15.56; %H, 3.47; %N 6.49. ESI-MS: m/z = 265.9 $[M\text{-}H_2O]^+$; ν_{max} (KBr)/cm^{-1} V=O 949.

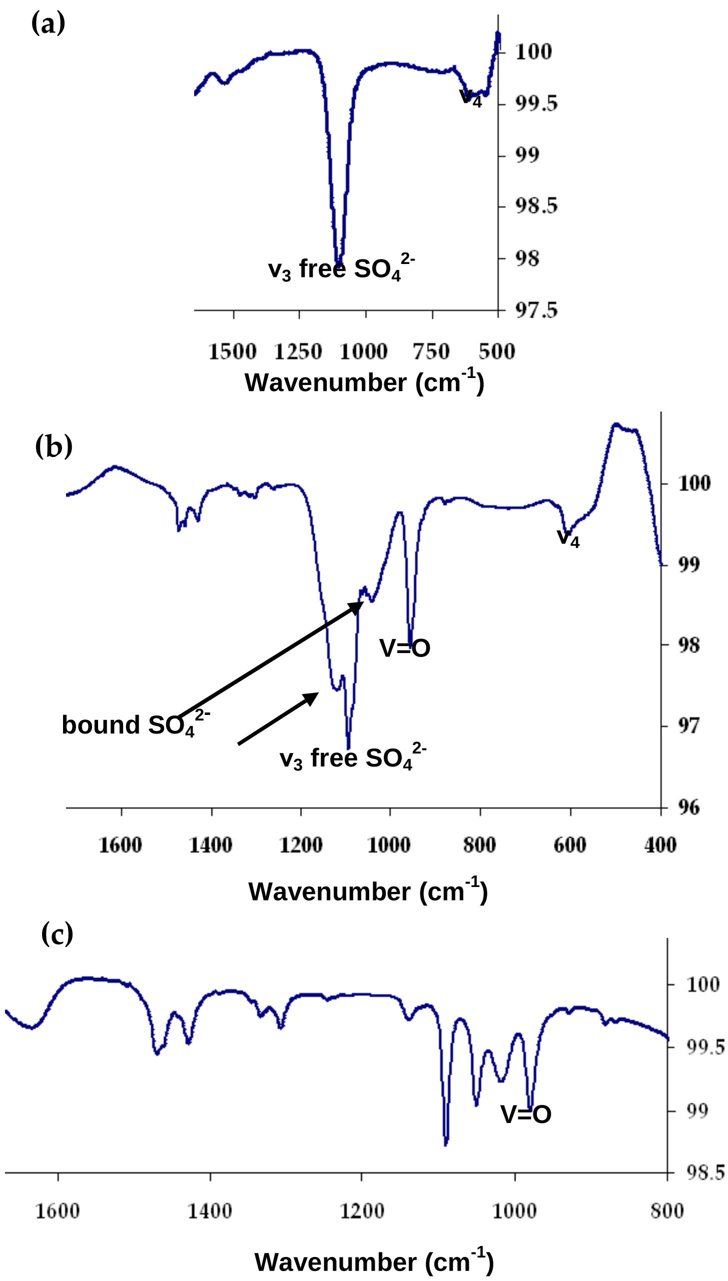
Oxovanadium(IV)-1-1'-[1,4-phenylenebis(methylene)]-bis(1,4,8,11-tetraazacyclotetradecane)·4PF$_6$

Oxovanadium(IV)-bicyclam chloride (4) (30.25 mg, 0.04 mmol) was dissolved in 8 mL HPLC Grade methanol at room temperature. An aqueous solution (2 mL) of silver hexafluorophosphate (40.45 mg, 0.16 mmol, 4 mol. equiv.) was added and an instant white precipitate was observed. The reaction was stirred at room temperature for 16 h. The solution was separated under centrifugal force (4000 rpm, 30 min) resulting in a green solution and white solid. The green solution was filtered and the solvent removed under reduced pressure. The product was further dried under vacuum and dried to a green powder (10 mg, 0.02 mmol, 40%). Anal. Calc. for $C_{28}H_{58}N_4V_2O_4{\cdot}4PF_6{\cdot}CH_3OH$ %C, 27.11; %H, 4.86; %N, 8.72. Found %C, 27.95; %H, 5.20; %N 8.12. ESI-MS: m/z = 637.2 $[M\text{-}2H_2O]^+$; ν_{max} (K/Br)cm^{-1} V=O 966.

5. Solution IR and conductivity measurements

Solution IR spectra for (a) $MgSO_4$ (standard) and oxovanadium(IV) cyclam complexes (b) **1** (sulfate) and (c) **2** (chloride)

Figure S5. Solution IR and conductivity



Published experimental values for conductivity measurements of electrolytes in water[2] provide an indication of ranges that may be expected from different ratios of electrolytes in solution.

Expected Molar Conductance (Λ_M) Ranges[a] for 2, 3, 4 and 5 Ion Electrolytes (~10^{-3} M) at 298 K

Solvent	Dielectric Constant	Electrolyte Types			
		1:1	2:1	3:1	4:1
Water [3]	78.4	118-131	235-273	408-435	~560

[a] Units on all molar conductivities are Ω^{-1} cm^2 mol^{-1}

As an example, the order of magnitude expected for neutral complexes is described in the literature as 5-6 Ω^{-1} cm^2 mol^{-1} for mixed-ligand complexes (1 x 10^{-3} M) of formula [M(bpy)(cbdca)] where M is Pd(II) or Pt(II).[4] Values for complexes **1** and **2** are listed in Table S5. Conductivity values for solutions increase in the order: complex 2 > $MgSO_4$ ~ NaCl > complex 1.

Table S5. Conductivity measurements for oxovanadium(IV) cyclam complexes (1, 2) and standards

	1 mM	0.1 mM
NaCl		
t = 0	135 (135)	160 (16)
t = 24 h	139 (139)	150 (15)
t = 60 h	140 (140)	160 (16)
t = 84 h	138 (138)	160 (16)
$MgSO_4$		
t = 0	186 (186)	-
t = 24 h	182 (182)	-
Complex 1		
t = 0	61 (61)	150 (15)
t = 24 h	61 (61)	150 (15)
Complex 2		
t = 0	247 (247)	-
t = 24 h	247 (247)	-

Units on all molar conductivities are Ω^{-1} cm^2 mol^{-1} and values in brackets represent measured conductivities, κ.

6. Crystallographic parameters

Table S6. Crystallographic parameters

(a) X-ray crystallographic data for oxovanadium(IV) cyclam complexes

Axial ligand *trans*- to V=O	**Sulfate (SO_4^{2-}), 1**	**Chloride (Cl^-), 2**
Formula	$C_{34}H_{84}N_{12}O_{19}S_3V_3$	$C_{11}H_{31}Cl_2N_4O_{3.5}V_1$
Formula weight	1214.13	397.24
Crystal system	Trigonal	Monoclinic
Space group	*R*3*c*	*Cc*
a / Å	25.2262(2)	15.3070(6)
b / Å	25.2262(2)	13.2387(6)
c / Å	15.1963(3)	18.7031(8)
α / °	90	90
β / °	90	101.165(2)
γ / °	120	90
Cell vol. / $Å^3$	8374.76(19)	3718.4(3)
Z	6	8
Density (Calc) mg/m^3	1.444	1.419
Abs. coeff. mm^{-1}	0.680	0.838
Reflections collected	55545	54922
Independent reflections	5575 [R(int) = 0.037]	8887 [R(int) = 0.048]
R1 (obs/all refl)	0.0292 [3992 data]	0.0543 [8478 data]
wR2 (obs/all refl)	0.0849	0.1491

(b) Selected bond lengths (Å) and angles (°) for oxovanadium(IV) cyclam complexes

Axial ligand *trans*- to V=O		**Sulfate (SO_4^{2-}), 1**	**Chloride (Cl^-), 2**
V-N bond lengths	N(1)-V(15) N(4)-V(15) N(8)-V(15) N(11)-V(15)	2.107(2) 2.114(2) 2.0841(19) 2.0976(19)	2.097(4) 2.097(4) 2.081(4) 2.082(4)
V=O bond lengths	V(15)-O(16)	1.6093(17)	1.599(3)
V-L* bond lengths		2.1359(16) V(15)-O(17)	2.6501(12) V(15)-Cl(17)
Bond angles	N(1)-V-N(11)	95.98(8)	95.67(16)
	N(4)-V-N(1)	84.27(9)	83.91(15)
	N(4)-V-N(8)	92.92(8)	92.12(15)
	N(8)-V-N(1)	166.88(7)	165.46(16)
	N(1)-V-L*	93.92(9)	83.39(12)
	L-V=O	177.83(9)	176.99(12)

* L = bonding atom of axial ligand trans- to V=O.

7. References

(1) Pannecouque, C.; Daelemans, D.; De Clercq, E. *Nat. Protocol.* **2008,** *3*, 427-434.

(2) Angelica, R. J. *Synthesis and Technique in Inorganic Chemistry*. 2 ed.; W B Saunders Company: Philadelphia, 1977.

(3) Sneed, M.; Maynard, J., *General Inorganic Chemistry*. Van Nostrand: New York, 1942; p 813.

(4) Mansuri-Torshizi, H.; Ghadimy, S.; Akbarzadeh, N. *Chem. Pharm. Bull.* **2001,** *49*, 1517-1520.