Pergamon

PII: S0277-5387(97)00056-9

Structural and conformational analysis of Tc^V and Re^V dioxo complexes. X-ray crystal structure of $[TcO_2(tn)_2]I \cdot H_2O$

Carlos Kremer,[a]* Jorge Gancheff,[a] Eduardo Kremer,[a] Alvaro W. Mombrú,[b]
Oscar González,[b] Raul Mariezcurrena,[b] Leopoldo Suescun,[b] Maria L. Cubas[c]
and Oscar N. Ventura[c]

[a]Cátedra de Química Inorgánica, Facultad de Química, CC 1157, Montevideo, Uruguay

[b]Laboratorio de Cristalografía, Cátedra de Física, Facultad de Química, CC 1157, Montevideo, Uruguay

[c]MTC-Lab, Facultad de Química, CC 1157, Montevideo, Uruguay

Abstract—$[Tc^VO_2(tn)_2]I$ (tn = trimethylenediamine) was prepared from direct reduction of TcO_4^- with dithionite in presence of the ligand. The crystal structure of $[TcO_2(tn)_2]I \cdot H_2O$ was determined from X-ray data. It consists on a squashed octahedron with Tc—O bond lengths of 1.784 and 1.754 Å conforming a TcO_2^+ core. The amines lie in the equatorial plane, almost perpendicular to the core. Conformational analyses of several analogous *trans*-M^V dioxo complexes (M = Tc, Re) was performed by molecular mechanics and semiempirical calculations. Energy differences between possible conformers are low. Therefore, a mixture of different conformers is expected to be found in solution. © 1997 Elsevier Science Ltd

Among the various metals used for medical purposes, Tc and Re are (and will be in the foreseeable future) two of the most developed ones. Tc, as ^{99m}Tc, remains the most widely used due to favourable physical properties (6 h half life, 140 keV γ-ray emission), ready availability (through $^{99}Mo/^{99m}Tc$ generators) and rather low cost [1]. In recent years, attention has been also focused on the Re analogous complexes, because ^{186}Re offers good physical properties (3.8 days half life, 1.08 MeV maximum $β^-$ ray energy) for radiotherapy purposes [2].

One of the most important tasks in this field is to find quantitative structure–activity relationships (QSAR), i.e. in which way structure and conformation determine the biological behaviour of these labelled molecules. For example, it is well known that brain trapping of ^{99m}Tc-HMPAO (HMPAO = hexamethylpropyleneamineoxime) is stereospecific [3]. Therefore, to obtain detailed information about the stereochemical disposition of the ligands (performing conformational studies) is of utmost importance in order to obtain a deeper insight into QSAR.

As these studies are very difficult to perform at radiopharmaceutical scale (nanomolar concentration of the species), analysis with ^{99}Tc and stable Re samples are performed at millimolar scale usually. In this way, compounds can be isolated and analyzed by X-ray diffraction techniques. However, it seems clear that atomic arrangement of the molecules in the solid state is not the unique point that determines QSAR. Conformation of the complexes could be very different in solution, where interactions with the solvent and ions, and a greater flexibility of the molecule could result in a different reactivity.

Theoretical calculations appear as a useful tool to study this side of the reactivity of the Tc/Re radiopharmaceuticals. Only a few papers exist dealing with this aspect, mostly focused on the molecular modelling of radiopharmaceuticals [4,5].

Technetium and rhenium belong to the same group of the periodic table. The analogy of Tc–Re has been used to deduce much information about their coordination compounds [6,7]. Specially, the strong resem-

---

* Author to whom correspondence should be addressed.

blance in the structure of the complexes is remarkable. In this work, we performed the analysis of the structure and conformation of some M^V dioxo complexes (M = Tc, Re) with polyamines. It is well known [8–10] that M^V metallic centres form a distorted octahedral arrangement with two oxo groups in *trans* position and the four equatorial positions occupied by N atoms belonging to one or two polyamines. Among complexes with this structure, Re-en [11] (en = 1,2-diaminoethane), Re-tn [12] (tn = trimethylenediamine), Re-cyclam [13,14] (cyclam = 1,4,8,11-tatraazacyclotetradecane), Tc-en [15] and Tc-cyclam [16] were studied by X-ray diffraction analysis. In order to complete the structural data, we have resolved the structure of the complex Tc-tn. With these results, the six structures were compared.

As ligands, en, tn and cyclam can exist in the complexes in different conformations. Molecular mechanics and semiempirical calculations were also performed to study the relative stability of the conformers.

EXPERIMENTAL

Materials

^{99}Tc, as NH_4TcO_4, was purchased from Amersham International (England). Precautions for handling this material are described elsewhere [17,18]. All other materials were of reagent grade and used as received.

Synthesis of [TcO$_2$(tn)$_2$]I

The Tc complex was synthesized following general trends previously reported [19]. A mixture of an aqueous solution (2 cm^3 0.031 M) of NH_4TcO_4 (0.062 mmol), tn (0.2 cm^3, 2.4 mmol) and $Na_2S_2O_4$ (40 mg, 0.23 mmol) was allowed to react for 45 min at room temperature. To this pink solution containing [TcO$_2$(tn)$_2$]$^+$, a large excess of NaI (3 g dissolved in 2 cm^3 of water) was added. The solution was kept at 4°C overnight. The final pink solid was obtained in 70–75% yield. It was checked by Tc and I elemental analysis and its IR and UV–vis spectra were compared with those reported.

Suitable crystals for X-ray diffraction studies were obtained by slow diffusion of an aqueous solution into ethanol.

X-ray diffraction

Crystal data. $C_6H_{22}O_3N_4TcI$, $M = 424.18$, orthorhombic, $a = 14.873(2)$, $b = 16.994(2)$, $c = 5.5945(5)$ Å, $U = 1414.0(3)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $D_c = 1.992$ g cm^{-3}, $\mu(Mo-K_\alpha) = 2.265$ mm^{-1}, $F(000) = 824$, crystal size $0.25 \times 0.10 \times 0.10$ mm.

Structure determination. Data were collected at room temperature on a Rigaku AFC7S four-circle

diffractometer in the range $2.40 \leqslant \theta \leqslant 24.98°$, $-17 \leqslant h \leqslant 17$, $-20 \leqslant k \leqslant 20$, $-6 \leqslant l \leqslant 6$. 2314 reflections were collected in the 2θ–ω scan mode, of which 2086 were unique ($R_{int} = 2.49\%$) and 1926 [$I > 2\sigma(I)$] were used in the full-matrix least-squares refinement with the SHELXL-93 [20] program. The structure was solved using direct methods with the SHELXS-86 [21] program. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms belonging to —CH$_2$ groups were included at calculated positions in rigid tetrahedral geometry for secondary carbon atoms, with C—H bond distance 0.97 Å. The other hydrogen atoms were found experimentally [N—H 0.82(2) and O—H 0.99(7) Å for the water molecule]. Hydrogen atoms were refined isotropically with equivalent H atoms with equal U_{iso} factors. Final residuals were $R = 0.0313$ for a weighting scheme of $w - 1 = [\sigma^2(F_0^2) + (0.0543P)^2 + 0.45P]$, where $P = (F_0^2 + 2F_c^2)/3$. The goodness-of-fit (Goof) finished at 1.111. Mean final shift/esd was 0.000. The maximum and minimum residual densities were 1.156 and -1.514 e Å^{-3}, respectively.

Calculations

Conformational analyses were performed by molecular mechanics (MM) and semiempirical (ZINDO) calculations, implemented in the Hyperchem package.

Molecular mechanics (MM) calculations were performed using the MM+ force field, a proprietary extension of the MM2 force field developed by Allinger *et al.* [22]. It is primarily designed for small organic molecules although has been expanded to other systems [23]. No parameters are available in the literature for either Tc or Re. Therefore, default standard parameters were employed.

Semiempirical calculations were performed with ZINDO/1 method, a modified version of the intermediate neglect of differential overlap (INDO), originally introduced by Pople *et al.* [24–28]. Zerner's original INDO/1 used the Slater orbital exponents with a distance dependence for the first-row transition metals only. However, constant orbital exponents are used in Hyperchem for all the available elements (included Tc but not Re) as recommended by Anderson *et al.* [29].

Atomic charges were calculated using the Mulliken population analysis.

All self consistent field (SCF) calculations were of the closed-shell restricted Hartree–Fock type (RHF) and carried out on a IBM RS 6000 workstation.

RESULTS AND DISCUSSION

Selected bond distances and angles for [TcO$_2$(tn)$_2$]I · H$_2$O are given in Table 1. Tables of coordinates, anisotropic temperature factors, hydrogen atom coordinates and a full listing of geometric data are available as supplementary data. Three monomers linked

Table 1. Selected bond lengths (Å) and angles (°) for
[TcO$_2$(tn)$_2$]I · H$_2$O

Tc—O(1)	1.748(4)
Tc—O(2)	1.754(4)
Tc—N(2A)	2.163(5)
Tc—N(1A)	2.173(5)
Tc—N(1B)	2.175(5)
Tc—N(2B)	2.179(5)
O(1)—Tc—O(2)	179.4(2)
O(1)—Tc—N(2A)	90.3(2)
O(2)—Tc—N(2A)	90.1(2)
O(1)—Tc—N(1A)	89.7(2)
O(2)—Tc—N(1A)	90.7(2)
N(2A)—Tc—N(1A)	90.0(2)
O(1)—Tc—N(1B)	90.5(2)
O(2)—Tc—N(1B)	89.1(2)
N(2A)—Tc—N(1B)	90.4(2)
N(1A)—Tc—N(1B)	179.6(2)
O(1)—Tc—N(2B)	89.8(2)
O(2)—Tc—N(2B)	89.8(2)
N(2A)—Tc—N(2B)	179.9(2)
N(1A)—Tc—N(2B)	90.0(2)
N(1B)—Tc—N(2B)	89.6(2)
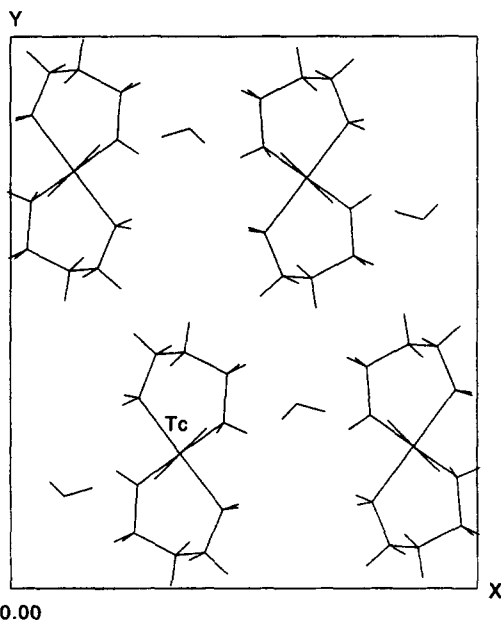
Fig. 2. Crystal packing along the c axis.

by water mediated hydrogen bonds are shown in Fig. 1 [30], along with the labelling scheme used. A view of the packing along the c axis is shown in Fig. 2. The packing consists of monomeric units of the central ion with two chelating tn ligands in an equatorial plane and two oxo groups in axial positions, linked by hydrogen bonds with water solvent molecules forming linear chains of canted units along the x direction.

The links are established between the oxo ligands and the water solvent molecules [O(1) and O(3) through H(1), and O(2) and O(3) through H(2)], as shown by the distances O(1)—H(1) 2.5(1) and

O(2)—H(2) 2.0(1) Å. There is evidence for additional hydrogen bonds linking monomeric units through iodide counterion, mediated by the primary amine groups with the mean distance 2.9(1) Å, I—H(2AB), I—H(2BA) and I—H(2BB). Monomeric units are also linked by hydrogen bonding through one of the oxo ligands O(2) and H(1BA) from an amine group, with the distance O(2)—H(1BA) 2.1(1) Å.

The coordination polyhedron around central Tc^V ion can be described as a squashed octahedron. Bond lengths for Tc—O are 1.748(4) Å for O(1) and 1.754(4) Å for O(2), very similar to those previously reported (see Table 2). Tc—N distances range from 2.163(5) Å for N(2A) to 2.179(5) Å for N(2B). The
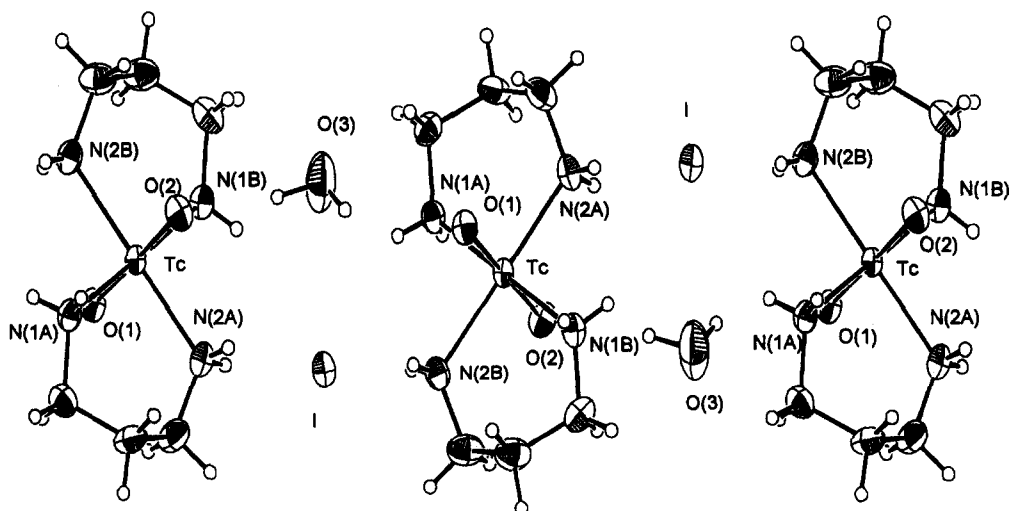

Fig. 1. Three monomeric units and their positions related to iodide ions and water molecules. Non-hydrogen atoms shown as ellipsoids at the 40% probability level.

Table 2. Structural data of trans-dioxo M^V complexes

Compound	d_{M-O} (Å)	Angle O—M—O (°)	d_{M-N} (Å)	Angle N—M—N (°)	d_{N-N} (Å)	Angle N—C—C (°)	Ring conformation	Ref.
$[ReO_2(en)_2]Cl$	1.769	179.3	2.154	80.0	2.82	107.5	$\lambda\delta$	[11]
	1.761		2.150	79.3		108.5		
			2.152					
			2.191					
$[ReO_2(tn)_2]I \cdot H_2O$	1.786	177.0	2.156	89.5	3.01	114	chair, parallel	[12]
	1.749		2.108	92.1		110		
			2.156					
			2.173					
$[ReO_2(cyclam)]PF_6$	1.78	a	2.09	97.1^c	3.20^c	a	chair, parallel^c	[13]
	1.77		2.15	82.9^b			$\lambda\delta^b$	
$[ReO_2(cyclam)]ReO_4 \cdot 1/4H_2O$	1.775	180.0	2.136	97.0^c	3.22^c	a	chair, parallel^c	[14]
			2.141	83.0^b	2.86^b		$\lambda\delta^b$	
$[TcO_2(en)_2]Cl$	1.752	178.6	2.146	80.37	2.82	109.7	$\delta\delta/\lambda\lambda$	[15]
	1.741		2.181	79.97		111.7		
			2.140					
			2.165					
$[TcO_2(tn)_2]I \cdot H_2O$	1.784	179.4	2.163	90.0	3.07	111.9	chair, parallel	This
	1.754		2.173	89.6		112.1		work
			2.175					
			2.179					
$[TcO_2(cyclam)]ClO_4 \cdot H_2O$	1.749	a	2.130	96.2^c	3.00^c	112.1	cyclam(III)	[16]
			2.119	2.85^b				

^{a} Not reported.
^{b} For the five-membered ring.
^{c} For the six-membered ring.

bidimensionality of octahedral mean planes proved to be in agreement with the description of an undistorted squashed octahedron. The O=Tc=O moiety is nearly lineal and perpendicular to the plane determined by the four nitrogens.

The chelating tn ligands rings show rather distorted chair conformation antisymmetric with each other in the same monomeric unit [puckering amplitude $Q = 0.563(7)$ and $0.589(7)$ Å, theta $= 17.3(6)$ and $162.5(6)°$, phi $= 178.1(22)$ and $0.2(21)°$ for both six membered rings] [31]. This is also the case in the Re^V analogue [12]. As previously stated [32], this conformation is expected to be the most stable for this ligand, compared with boat and twist forms.

It is very interesting to analyse N—C—C angles as a measure of bond strain within the coordinated ligands. Taking into account M—N bond lengths (M = Tc, Re) and N—M—N angles, the distances between nitrogens belonging to the same ring can be calculated (see Table 2). For an unstrained didentate en, the ideal bite size (N—N distance in the ring) is 2.8 Å, while for tn, a shorter distance of 2.5 Å is ideal [33]. Re-en and Tc-en complexes fit the ideal bite size, resulting in a rather unstrained ligand with N—C—C angles close to the theoretical value 109.5°. On the other hand, tn complexes have N—N distances much higher than 2.5 Å (always longer than 3.0 Å), leading to an opening of the N—C—C angles. In the case

of $[TcO_2(tn)_2]I \cdot H_2O$, these angles are 111.9(5) and 112.1(5)°.

The en, tn and cyclam ligands offer the possibility to form complexes in different conformations. Each ethylenediamine chelate ring can adopt either δ or λ chirality. So, for trans-$[MO_2(en)_2]^+$ complexes, $\delta\lambda$, $\lambda\lambda$ and $\delta\delta$ configurations are possible. The last two configurations are energetically equivalent. As shown in Table 2, $[ReO_2(en)_2]Cl$ has a $\delta\lambda$ conformation in the solid state, while $[TcO_2(en)_2]Cl$ exhibits equal population of the $\delta\delta$ and $\lambda\lambda$ enantiomers. It was also reported that $[TcO_2(en)_2]I$ has a $\delta\lambda$ conformation [15]. It is possible to study the relative stability of these conformers using molecular mechanics calculations, which show that the three conformations are not very different in energy. If the semiempirical method ZINDO/1 is used for Tc-en complex, an energy difference of 0.3 kcal mol^{-1} is found, the $\delta\lambda$ conformation being less stable than $\lambda\lambda$ and $\delta\delta$. This difference can be attributed to a change from staggered to eclipsed —NH$_2$ groups. As previously reported [34], these conformations could be separated by an energy barrier corresponding to an envelope transition state in which dihedral angle between NCC and CCN planes is 0° (labelled "plane" in Table 2). This state is clearly less stable than the others. Consequently, it is not expected that enantiomer predominates any one in solution. In the solid state,

Table 3. Calculated energy (in kcal mol^{-1}) using molecular mechanics (E_{MM}) and ZINDO/1 (E_Z) for the different conformers

Compound	Conformer	E_{MM}	E_Z (ΔH_f)
[TcO$_2$(en)$_2$]$^+$	$\delta\lambda$	8.96	-3662.9
	$\lambda\lambda$	8.96	-3663.2
	Plane	15.80	—
[ReO$_2$(en)$_2$]$^+$	$\delta\lambda$	8.49	—
	$\lambda\lambda$	8.49	—
	Plane	15.39	—
[TcO$_2$(tn)$_2$]$^+$	$\delta\lambda$	21.04	-4761.5
	$\lambda\lambda$	21.00	-4762.3
	Chair, parallel	14.50	-4888.2
	Chair, antiparallel	19.07	-4888.1
[ReO$_2$(tn)$_2$]$^+$	$\delta\lambda$	7.11	—
	$\lambda\lambda$	3.94	—
	Chair, parallel	13.94	—
	Chair, antiparallel	14.48	—
[TcO$_2$(cyclam)]$^+$	Cyclam(I)	57.51	-6864.7
	Cyclam(II)	57.54	-6870.6
	Cyclam(III)	22.03	-6880.5
	Cyclam(IV)	60.52	-6856.8
[ReO$_2$(cyclam)]$^+$	Cyclam(I)	50.03	—
	Cyclam(II)	57.51	—
	Cyclam(III)	21.10	—
	Cyclam(IV)	59.48	—

Table 4. Atomic charges (using Mulliken analysis) for the main atoms in the different species

Compound	Atom	Atomic charge
en	N	-0.34
Tc-en	N	-0.173
	O	-0.342
	Tc	0.168
tn	N	-0.33
Tc-tn	N	-0.172
	O	-0.347
	Tc	0.139
cyclam	N	-0.255
Tc-cyclam	N	-0.111
	O	-0.371
	Tc	0.208

relative stability can be influenced by packing energies, counterions, etc., and so, different situations are found in Tc and Re complexes.

For a M-tn complex, a chair conformation of the ring is expected to be the most stable. For a bis tn complex, the way CCC planes are folded defines the parallel and antiparallel conformers [32]. In the case of [TcO$_2$(tn)$_2$]$^+$, semiempirical calculations give an energy difference of only 0.1 kcal mol^{-1} between them. When rings are forced to adopt a twist form (com-

bination of δ and λ conformations), total energy increases, losing stability in the complex. Once more, this difference is not enough to infer the predominance of any given isomer in solution.

For the cyclam ligand, the situation is more complicated because five and six membered rings are formed. It is convenient to discuss the configuration of the coordinated ligand based on the direction of the N—H bonds [35]. Hence, four isomers are possible: cyclam(I), in which a five-membered ring adopts a plane disposition and the other three rings a δ conformation, cyclam(II) with a $\delta\delta\lambda\lambda$ conformation, cyclam(III) with five-membered rings in λ conformation and six-membered in chair conformation, and cyclam(IV) with $\lambda\lambda\delta\delta$ conformation. Energy calculations (Table 3) show that the M-cyclam(III) conformer is always more stable than the others. For the [TcO$_2$(cyclam)]$^+$ complex, the cyclam(III) conformer is ~ 10 kcal mol^{-1} more stable than the cyclam(II) conformer.
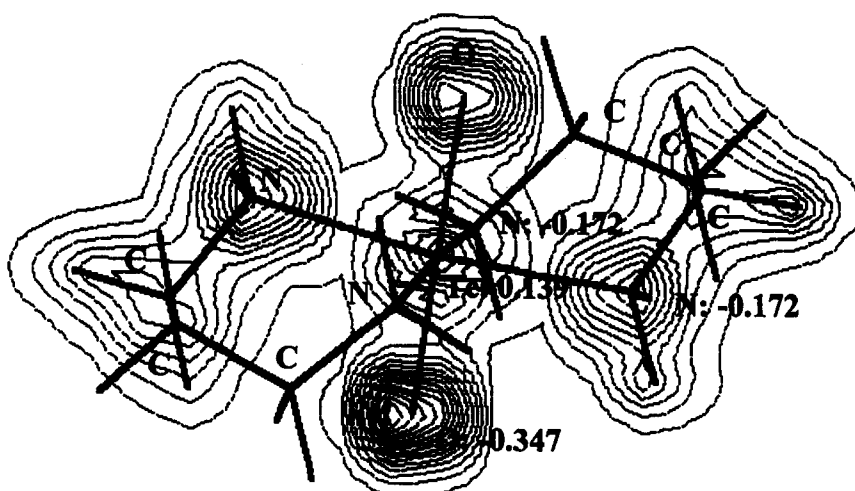

Fig. 3. Contour plots of the electron density and atomic charge values of the atoms for the most stable conformer of [TcO$_2$(tn)$_2$]$^+$.

It is very interesting to analyse the charge on the different atoms in the complex. This is shown in Table 4 and Figure 3. It is well known that these complexes can be easily protonated. In the Re compounds, pK_a values can be determined, but not in the Tc analogous due to their instability [12,36]. It is assumed (essentially by spectroscopic determinations) that protonation occurs at the oxo group. From our results, it is clear that oxo groups are the points of the molecule with higher electron density. By comparison with the free ligands, displacement of the electron density on N to the metallic center (to establish the coordination) can be observed.

REFERENCES

1. Jurisson, S., Berning, D., Jia, W. and Ma, D., *Chem. Rev.*, 1993, **93**, 1137.
2. Hashimoto, K. and Yoshihara, K., *Topics Curr. Chem.*, 1996, **176**, 275.
3. Volkert, W. A. and Jurisson, S., *Topics Curr. Chem.*, 1996, **176**, 123.
4. Vitale, A. A., Calviño, M. A., Ferrari, C. C., Stahl, A. E. and Pomilio, A. B., *J. Labelled Compd. Radiopharm.*, 1995, **36**, 509.
5. Hancock, R. D., Reichert, D. E. and Welch, M. J., *Inorg. Chem.*, 1996, **35**, 2165.
6. Peacock, R. D., *The Chemistry of Technetium and Rhenium*. Elsevier, Amsterdam, 1966.
7. Gambino, D., Kremer, C., Cartesio, S., León, A., León, A. and Kremer, E., *J. Radioanal. Nucl. Chem., Lett.*, 1989, **136**, 341.
8. Johannsen, B. and Spies, H., *Topics Curr. Chem.*, 1996, **35**, 77.
9. Schwochau, K. and Pleger, U., *Radiochim. Acta*, 1993, **63**, 103.
10. Conner, K. A. and Walton, R. A., in *Comprehensive Coordination Chemistry*, Vol. 4, ed. G. Wilkinson. Pergamon Press, Oxford, 1987, pp. 125–213.
11. Lock, C. J. L. and Turner, G., *Acta Cryst.*, 1978, **B34**, 923.
12. Kremer, C., Kremer, E., Domínguez, S., Chinea, E., Mederos, A. and Castiñeiras, A., *Polyhedron*, 1996, **15**, 4341.
13. Alvarez, S., Bolzati, C., Duatti, A., Zucchini, G. L., Bandoli, G. and Refosco, F., *Inorg. Chem.*, 1992, **31**, 2595.
14. Wang, Y. P., Che, C. M., Wong, K. Y. and Peng, S. M., *Inorg. Chem.*, 1993, **32**, 5827.
15. Kastner, M. E., Lindsay, M. J. and Clarke, M. J., *Inorg. Chem.*, 1982, **21**, 2037.
16. Zuckman, S. A., Freeman, G. M., Troutner, D. E., Volkert, W. A., Holmes, R. A., Van der Veer, D. G. and Barefield, E. K., *Inorg. Chem.*, 1981, **20**, 2386.
17. Schwochau, K., *Radiochim. Acta*, 1983, **32**, 139.
18. Eckelman, W. C. and Volkert, W. A., *Int. J. Appl. Radiat. Isot.*, 1982, **33**, 945.
19. Fackler, P. H., Lindsay, M. J., Clarke, M. J. and Kastner, M. E., *Inorg. Chim. Acta*, 1985, **109**, 39.
20. Sheldrick, G. M., *SHELXL93. Program for the Refinement of Crystal Structures.* University of Göttingen, Germany, 1986.
21. Sheldrick, G. M., *Acta Cryst.*, 1990, **A46**, 467.
22. Allinger, N. L., *J. Am. Chem. Soc.*, 1977, **99**, 8127.
23. Lipkowitz, K. B., *QCPE Bulletin*, Indiana University, 1992, **12**, 1.
24. Pople, J. A., Santry, D. P. and Segal, G. A., *J. Chem. Phys.*, 1965, **43**, S129.
25. Pople, J. A. and Segal, G. A., *J. Chem. Phys.*, 1965, **43**, S136.
26. Pople, J. A. and Segal, G. A., *J. Chem. Phys.*, 1966, **44**, 3289.
27. Santry, D. P. and Segal, G. A., *J. Chem. Phys.*, 1967, **47**, 158.
28. Pople, J. A., Beveridge, D. L. and Dobosh, P. A., *J. Chem. Phys.*, 1967, **47**, 2026.
29. Anderson, W. P., Edwards, W. D. and Zerner, M. C., *Inorg. Chem.*, 1986, **25**, 2728.
30. Zsolnai, L., *XPMA. Molecular Geometry Program for PC.* University of Heidelberg, Germany, 1996.
31. Cremer, D. and Pople, J. A., *J. Am. Chem. Soc.*, 1975, **97**, 1354.
32. Jurnak, F. A. and Raymond, K. N., *Inorg. Chem.*, 1972, **11**, 3149.
33. Hancock, R. D., *Prog. Inorg. Chem.*, 1989, **37**, 187.
34. Gollogly, J. R., Hawkins, C. J. and Beattie, J. K., *Inorg. Chem.*, 1971, **10**, 317.
35. Bosnich, B., Poon, C. K. and Tobe, M. L., *Inorg. Chem.*, 1965, **4**, 1102.
36. Kremer, C., Domínguez, S., Pérez-Sánchez, M., Mederos, A. and Kremer, E., *J. Radioanal. Nucl. Chem., Lett.*, 1996, **213**, 263.