Inorg. Chem. **1996,** *35,* 2165−2166

Molecular Mechanics Force Field for Modeling Technetium(V) Complexes

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Received November 2, 1995

Technetium radiopharmaceuticals, as complexes of the ^{99m}Tc radioisotope, are of great importance in diagnostic nuclear medicine.[1,2] There are intensive efforts underway into the development of Tc^{V}O complexes for radiopharmaceutical use which mimic receptor agonists or antagonists such as steroids and neuroreceptor probes.[3−8] This communication reports a MM model of square pyramidal complexes of the Tc^{V}O group, incorporating a novel feature in MM calculations on coordination compounds, fairly large torsional barriers to rotation (V_i) about the Tc−L (L = donor atom) bonds. Typically the torsional barriers of metal to donor atom bonds are quite small to non-existent; these large barriers are interpreted in terms of significant Tc−L π-bonding.

In spite of reports of MM models of complexes of a variety of metal ions in recent years,[9−13] and usefulness of MM in ligand design,[9−13] few reports exist of force field parameters that allow for modeling Tc complexes.[14] Possibly the most important technetium complexes are those of Tc(V) with a single oxo group attached to Tc. These have[15,16] a square pyramidal structure. The four donor atoms other than the oxo group form a square plane, with the Tc some 0.7 Å above this plane, and the Tc═O bond at right angles to the plane. These features of Tc^{V}O complexes are readily reproduced in MM with a covalent[9−13] description of the bonding, where specific L−Tc−L angles are defined with associated angle deformation force constants. What is difficult to reproduce is the general feature that, for example, ethylene bridges of the DME ligands in [TcO(DME)$_2$]$^-$ do not lie symmetrically about the plane created by the Tc and two S donor atoms of the ligand, but are inclined out of this plane towards the Tc═O group.

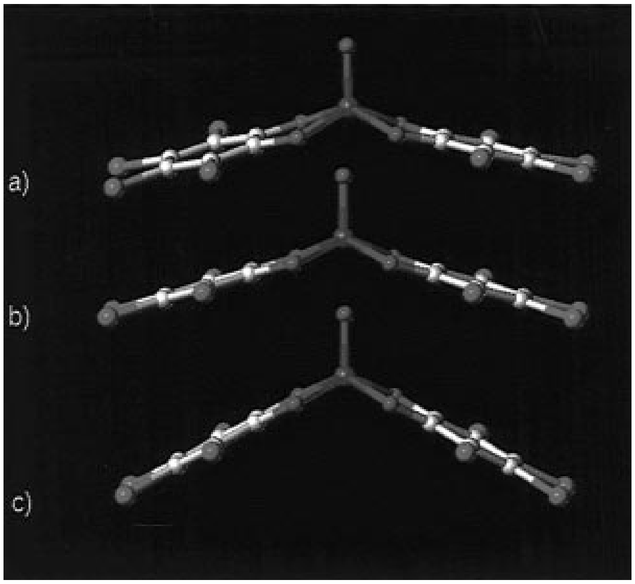

Figure 1. (a) Side-on view of the crystal structure of [TcO(TC)$_2$]$^-$ (TC = tetrachlorocatechol)(REFCODE: KIWJUV), to be compared with the MM generated structures (b) with O═Tc−O−C torsional paramaters included, and (c) set to zero. Color code for atoms: C, white; H, blue-green; N, blue; S, yellow; O, red; Tc, blue; Cl, green. Graphics were generated by SYBYL.[17]

The key to reproduction of this feature is the inclusion of torsion angles involving the oxo group oxygen, the Tc, L (which is S for DME), and carbon atom from the ligand. For [TcO(DME)$_2$]$^-$, the O═Tc−S−C torsion angle has an energy minima for rotation about the Tc−S bond when the Tc═O and S−C bonds are at right angles to each other. This aspect of the structure of complexes of Tc^{V}O is demonstrated clearly, where unidentate ligands such as thiophenol or thioureas[20a,b] are coordinated to Tc. The O═Tc−S−C torsion angles of these complexes are close to 90°, even without chelate bridges to constrain the S−C bond of the ligand to give O═Tc−S−C torsion angles near 90°.

An interpretation of Tc−S bonding that accounts for these O═Tc−S−C torsion angles is that these reflect significant overlap between filled *p* orbitals on the sulfurs and the oxygen atoms, and d$_{yz}$ or d$_{zx}$ orbitals on the Tc. Zuckman et al.[18] have proposed that L to M π-bonding is important in the Tc−L bonds of square pyramidal complexes of the Tc^{V}O group. In support of the π-bonding interpretation, the need for torsional constants of this type arises only for donor atoms with filled p-orbitals suitable for L−M π-bonding, such as thiol S, deprotonated amide nitrogen, or phenolic oxygen.

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0020-1669/96/1335-2165$12.00/0

Table 1. MM Parameters for Modeling $TcOL_4$ Complexes[a]

Bond Length Deformation Constants[b]

	Tc−S	Tc−N(am)[c]	Tc−N(sp^3)[d]	Tc=O	Tc−O[e]
equilib length Å	2.33	1.91	2.20	1.65	1.96
K_B[f]	200	200	100	400	200

Bond Angle Deformation[g]

	O=Tc−S	O=Tc−N(am)[c]	O=Tc−N(sp^3)[d]
equilib angle (deg)	109.1	109.1	110.0

	O=Tc−O[e]	Tc−S−C	S−Tc−S(trans)	S−Tc−S(cis)	N(sp^2)−Tc−N(am)
equilib angle (deg)	108.9	98.0	142.0	82.1	140.0

Torsional Constants

	O=Tc−S−C	O=Tc−N(am)−C
torsional barrier (kcal mol^{-1})	3.5	3.5

[a] These parameters are to be used in the SYBYL program in conjunction with the TAFF force field.[17] The parameter set is not complete because of space limitations. [b] Units for equilibrium bond length are in Å, and for bond length deformation force constants (K_B) are in kcal mol^{-1} Å^{-1}. [c] N(am) = deprotonated amide nitrogen. [d] sp^3 hybridized deprotonated polyamine nitrogen. [e] Phenolic oxygen. [f] There is little steric distortion of Tc−L bond lengths so these constants will be further refined as more strained structures become available. [g] Angle bending constants all presently as 0.008 kcal mol^{-1} deg^{-2}.

Preliminary ab initio calculations[19] (RHF/STO3-21G+) on $[TcO(DME)_2]^-$, found an MO with 32% contribution from the Tc, 43% from the oxygen, and from 4−2% from each of the sulfurs. Further support of this π-bonding hypothesis is that Tc−L bond lengths are shorter where π-bonding is postulated to occur, than where it is not. Thus, Tc−N(sp^2) and Tc−N(am) bonds are typically about 1.91 Å in length, whereas Tc−N for sp^3 hybridized N, and pyridine N, is typically about 2.20 Å in length. Thioether sulfurs also appear to form weaker π-bonds compared to deprotonated thiols, with Tc−S bonds some 0.06 Å longer for the thioether, and no apparent torsional barrier in the Tc−S(thioether) bond. The O=Tc−O−C torsional barrier for carboxylate oxygen is small, suggesting that the p electrons on this oxygen donor are much less available for π-bonding to the Tc than are those of phenolate oxygens. Those donors, which are postulated to be weak L to M π-bonders, sp^3 N, aromatic N, and carboxylate oxygen, all promote[15,16] the formation of Tc(V) complexes of coordination number six or higher, and the addition of a second oxo group. It appears that the Tc d orbitals can interact either with a second oxo group in the case of weak π-bonders, or through π-bonding in suitable donors. As might be expected, the O=Tc−S−C, O=Tc−O−C, and O=Tc−N−C (N = amide or sp^2 N) torsional barriers (V_i) of 3.5 kcal mol^{-1}, are smaller than V_i values in SYBYL[17] for modeling rotation about organic double bonds.

The parameters for modeling Tc(V) oxo complexes in Table 1, in conjunction with the TAFF force field,[17] reproduce structures of 35 complexes of the $TcOL_4$ type present in the literature[20] and Cambridge Structural Database.[21] Reference codes for those $TcOL_4$ complexes found in the Cambridge Database are given.[22] TheTc−L bond lengths of these complexes are reproduced with a standard deviation (σ) of 0.08 Å, L−Tc−L bond angles with $\sigma = 5.8°$ and O=Tc−L−C torsion angles with $\sigma = 12.2°$. The parameters in Table 1 were varied individually, with location of the minimum deviation for the MM predicted structural feature determined by the parameter, compared to the crystallographically determined feature, for each of the 35 structures. The parameters allow for modeling $TcOL_4$ complexes where L can be any combination of S (S of deprotonated mercaptans, or S of thioureas), the sp^2 hybridized nitrogen present in deprotonated amide nitrogens, deprotonated amine nitrogens, aromatic nitrogens, sp^3 hybridized saturated nitrogen, as well as the deprotonated oxygen donor of phenols.

The subtlety of structural detail that requires inclusion of O=Tc−L−C torsional contributions for accurate modeling is demonstrated in Figure 1b,c, where the crystal structure of the bis(tetrachlorocatechol) (TC) complex of Tc^VO (Figure 1a) is compared with the MM generated structures with (Figure 1b) and without (Figure 1c) inclusion of the torsional contribution.

The MM model described in this communication should prove useful in the development of new Tc-based radiopharmaceuticals. The candidate ligands for the synthesis of Tc^VO complexes which mimic biological substrates can be screened with the present MM model, greatly facilitating identification of potentially useful complexes. The development of this force field has also led to insight in the bonding interactions between the Tc(V) oxo group and donor atoms commonly used in ligands.

Acknowledgment. This work was supported by grants from the National Institutes of Health (CA 42925) and Mallinckrodt Medical, Inc.

Supporting Information Available: A table showing the standard deviations of the bond lengths, angles, and torsions for each tested complex and tables of the parameters for the SYBYL (TAFF) force field (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of this journal, can be ordered from the ACS, and can be downloaded by subscribers from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(22) Reference codes for $TcOL_4$ complexes taken from the Cambridge Structural Database are as follows: BATMTC, CEWZIN10, CILTAS, DATMUG, DORMUS, DORNAZ, DORNED, DORNIA, FISCIT, FIPJIX, FONNIF, FUYNES, GAXBAI, GEMNER, GIKZEF, JAVZAH, JAWMID, JEZTIR10, JIZBID, JOSSUF, KIWJUV, PATXTC, PCLTCC01, PEWTOA, PEXZIB, VULXAB, WACRUN, WEMKOO, and WEMKUU.