*Inorg. Chem.* **2002**, *41*, 2060–2069


# *De Novo* Structural Prediction of Transition Metal Complexes: Application to Technetium

**Corneliu Buda,[†] Stanley K. Burt,[‡] Thomas R. Cundari,*[,†] and Peter S. Shenkin[§]**

*Department of Chemistry, The University of Memphis, Computational Research on Materials Institute (CROMIUM), Memphis, Tennessee 38152, Advanced Biomedical Computing Center, National Cancer Institute-Frederick, Frederick, Maryland 21702, and Schrodinger, Inc., 120 West 45th Street, Suite 800, New York, New York 10036*

Received September 17, 2001

*De novo* structural prediction of transition metal complexes is investigated. Technetium complexes are chosen given their importance in medical imaging and nuclear waste remediation and for the chemical diversity they display. A new conformational searching algorithm (LIGB) for transition metals is described that allows one to search for different conformational *and* geometric isomers within a single simulation. In the preponderance of cases, both conformational searching techniques (LIGB and high-temperature molecular dynamics/simulated annealing) provide comparable results, while LIGB is superior for macrocyclic complexes. A genetic algorithm-optimized PM3(tm) parametrization for Tc is compared with the standard implementation and found to yield a significant improvement in predictive ability for the most prevalent Tc structural motifs. The utility of a coupled molecular mechanics–semiempirical quantum mechanics protocol is demonstrated for very rapid, efficient, and effective *de novo* prediction of transition metal complex geometries.

## Introduction

The first, and most important, step in any computer-aided design and analysis protocol is to determine reasonable geometries for target materials. The importance of molecular geometry is underscored by the tremendous value placed upon experimental techniques such as X-ray crystallography. Experiment is, however, primarily limited to stable materials with appreciable lifetimes that form in sufficient quantities to permit observation. Finally, experimental techniques are limited to chemical species that have already been synthesized and are amenable to experimental characterization. This fact, when combined with the tremendous recent increases in computational methods and technology, has resulted in an explosion in the use of modeling as an adjunct to experiment for the design and analysis of novel materials.

Modeling of transition metal (TM) complexes has lagged significantly behind that for organic moieties. These challenges arise from well-known difficulties inherent in transition metal chemistry:[1] large numbers of electrons and orbitals, relativistic and electron correlation effects, difficulties in modeling open-shell species, and "chemical diversity". The rational design of TM complexes must also deal with the extra isomeric complexity inherent in TM chemistry. In addition to conformational isomers arising from torsion about rotatable bonds, the conformational searching of metal complexes must generate and evaluate (1) geometric isomers (e.g., *cis* versus *trans* or *fac* versus *mer* octahedral complexes), (2) structural isomers (e.g., octahedral versus trigonal prismatic for six-coordinate complexes), (3) coordination isomers (e.g., apical and basal coordination sites for square pyramidal complexes), (4) spin "isomers" (typically for open-shell $d^2-d^8$ electronic configurations), and (5) linkage isomers (e.g., cyanide versus isocyanide, thiocyanate versus isothiocyanate, or mono- versus bidentate carboxylates).

The transition metals (TMs) play a pivotal role in biological applications. For example, metallodrugs are increasingly recognized as an important family of pharmaceuticals.[2] Important metallodrugs include platinum anticancer drugs,[3] gadolinium MRI contrast agents,[4] and technetium radiopharmaceuticals.[5] Over 85% of all radio-

* Author to whom correspondence should be addressed. E-mail: tcundari@memphis.edu.
[†] The University of Memphis.
[‡] ABCC, NCI-Frederick.
[§] Schrodinger, Inc.

(1) *Computational Organometallic Chemistry*; Cundari, T. R., Ed.; Dekker: New York, 2001.
(2) Berners-Price, S. J.; Sadler, P. J. *Coord. Chem. Rev.* **1996**, *151*, 1.
(3) *Platinum-Based Drugs in Cancer Therapy*; Kelland, L. R., Farrell, N. P., Eds.; Humana Press: Totowa, NJ, 2000.



10.1021/ic0109748 CCC: $22.00 
Published on Web 03/22/2002

pharmaceuticals now in clinical use are based on the metastable $^{99m}$Tc isotope. Transition metals also play a pivotal role in biochemistry, in particular, in enzymes. Well-known examples include heme metalloproteins for respiration and in vivo oxidation,[6] molybdenum oxidases,[7] blue copper enzymes,[8] and superoxide dismutase.[9]

Complexes chosen for study are those of technetium ($Z = 43$), the element situated in the middle of second transition series. Beginning in the 1970s, a large number of Tc compounds were synthesized and characterized.[5] Recently, there has been considerable interest in the conjugation of biomolecules to Tc radiopharmaceuticals (Tc-RPCs) to probe specific biological pathways.[5] The chemistry of Tc is also of relevance in connection with the environmental speciation and remediation of nuclear waste.[10] Considerable effort has been expended in the identification of Tc waste in government depositories, as well as viable remediation strategies.[10]

From a computational viewpoint, technetium has a rich "chemical diversity". Inspection of the Cambridge Structural Database (CSD[11]) reveals technetium complexes in a diverse array of formal oxidation states ($-1$ to $+7$), coordination numbers (four- through eight-coordination), ligating atom types (e.g., "soft" phosphorus and sulfur donors, as well as "hard" nitrogen and oxygen donors), and bond types (dative, single, and multiple). Technetium complexes also occur in a variety of spin states. Thus, Tc represents a very demanding test of computational methods aimed at effective and efficient *de novo* structural prediction. This is particularly so for very rapid approximate methods such as molecular mechanics[12] and semiempirical quantum mechanics,[13] which are typically best suited for describing a narrow range of highly related chemical entities.

There are several major goals for this research. First, a novel conformational searching technique (LIGB) specifically designed for metal complexes will be described. Second, a newly developed, genetic algorithm-optimized PM3(tm) parametrization, PM3(tm)-GA, will be compared with the standard parametrization, PM3(tm), for 197 Tc complexes, both mono- and polymetallic, in a diverse assortment of chemical environments. Third, two conformational searching methods for generating and evaluating different TM geometric isomers will be evaluated. Fourth, molecular mechanics (MM) and semiempirical quantum mechanics (SEQM) will be integrated into a *de novo* structural prediction protocol for TM complexes. Particular attention will be focused on Tc complexes with chemical motifs that are relevant to nuclear applications.

## Computational Methods

A molecular mechanics (MM) force field for Tc complexes has been reported by Cundari and Fu.[14] The MM force field was developed by genetic algorithm (GA) optimization of metric (equilibrium bond lengths and bond angles) and vibrational (force constants) parameters. The force field was developed for five- and six-coordinate Tc complexes. Newly defined ligating atom types include sp3 amine N, sp2 imine, enolate O, oxo O, phosphine P, chloride Cl, carboxylate O, sp2 amide N, and thiolate S. The force field incorporates standard bond stretching (harmonic), angle bending (harmonic), and dihedral torsion (three-term Fourier series) terms. Nonbonding interactions are modeled with a Buckingham potential. The coordination sphere of the Tc is modeled by replacing L−M−L angle bending terms with 1,3 van der Waals terms.[12,14] Metal−ligand bond lengths are not fixed in the MM optimization process.

A semiempirical quantum mechanics (SEQM) parametrization within the PM3(tm) Hamiltonian was optimized using a genetic algorithm (GA) approach.[15] A total of 21 PM3(tm) parameters are needed to describe each TM. These parameters include orbital exponents, bond integrals, electron−electron repulsions, core repulsion functions, and other entities needed to describe the electronic interactions of a Tc complex.

The force field and semiempirical parametrizations for Tc are generally able to reproduce experimental bond lengths and bond angles to within a few percent,[14,15] a level of accuracy commensurate with MM force fields for organic molecules and higher-level, ab initio calculations.[16]

Two molecular mechanics-based[14] conformational searching (CS) protocols were investigated. The first CS scheme involved


(4) (a) Reynolds, C. H.; Annan, N.; Beshah, K.; Huber, J. H.; Shaber, S. H.; Lenkinski, R. E.; Wortman, J. A. *J. Am. Chem. Soc*. **2000**, *122*, 8940. (b) Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev*. **1999**, *99*, 2293.

(5) (a) *Technetium − Chemistry and Radoipharmaceutical Applications*; Schwochau, K., Ed.; Wiley-VCH: Weinheim, 2000. (b) Jurisson, S. S.; Lydon, J. D. *Chem. Rev*. **1999**, *99*, 2205. (c) Heeg, M. J.; Jurisson, S. S. *Acc. Chem. Res*. **1999**, *32*, 1053. (d) Jurisson, S.; Berning, D.; Jia, W.; Ma, D. *Chem. Rev*. **1993**, *93*, 1137.

(6) (a) Hata, M.; Hirano, Y.; Hoshino, T.; Tsuda, M. *J. Am. Chem. Soc*. **2001**, *123*, 64100. (b) Collman, J. P.; Chien, A. S.; Eberspacher, T. A.; Brauman, J. I. *J. Am. Chem. Soc*. **2000**, *122*, 11098. (c) Toy, P. H.; Newcomb, M.; Coon, M. J.; Vaz, A. D. N. *J. Am. Chem. Soc*. **1998**, *120*, 9718. (d) Wertz, D. L.; Sisemore, M. F.; Selke, M.; Driscoll, J.; Valentine, J. S. *J. Am. Chem. Soc*. **1998**, *120*, 5331.

(7) (a) Izumi, Y.; Glaser, T.; Rose, K.; McMaster, J.; Basu, P.; Enemark, J. H.; Hedman, B.; Hodgson, K. O.; Solomon, E. I. *J. Am. Chem. Soc*. **1999**, *121*, 10035. (b) Raitsimring, A. M.; Pacheco, A.; Enemark, J. H. *J. Am. Chem. Soc*. **1998**, *120*, 11263.

(8) (a) Randall, D. W.; DeBeer, G., S.; Hedman, B.; Hodgson, K. O.; Fujisawa, K.; Solomon, E. I. *J. Am. Chem. Soc*. **2000**, *122*, 11620. (b) Bertini, I.; Fernández, C. O.; Karlsson, G. B.; Leckner, J.; Luchinat, C.; Malmström, B. G.; Nersissian, A. M.; Pierattelli, R.; Shipp, E.; Valentine, J. S.; Vila, A. *J. Am. Chem. Soc*. **2000**, *122*, 3701.

(9) (a) Wang, D.; Zhao, X.; Vargek, M.; Spiro, T. G. *J. Am. Chem. Soc*. **2000**, *122*, 2193. (b) Campbell, K. A.; Yikilmaz, E.; Grant, C. V.; Gregor, W.; Miller, A. F.; Britt, R. D. *J. Am. Chem. Soc*. **1999**, *121*, 471. (c) Edward, R. A.; Whittaker, M. A.; Whittaker, J. W.; Jameson, G. B.; Baker, E. N. *J. Am. Chem. Soc*. **1998**, *120*, 9684.

(10) (a) Bonnesen, P. V.; Moyer, B. A.; Presley, D. J.; Armstrong, V. S.; Haverlock, T. J.; Counce, R. M.; Sachleben, R. A. *Alkaline-side extraction of Technetium from tank waste using crown ethers and other extractants*; ORNL Report ORNL/TM-13241, June 1996. (b) Gula, M.; Harvey J. *Separation, concentration, and immobilization of Technetium and Iodine from alkaline supernate waste*; DOE Contract DE-AC21-97MC33137-43, March 1998. (c) Simmons, D. W. *An introduction to Technetium in the gaseous diffusion cascades*; ORNL report K/TSO-39, September 1996. (d) Blanchard, D. L.; Brown, G. N.; Conradson, S. D.; Fadeff, S. K.; Golcar, G. R.; Hess, N. J.; Klinger, G. S.; Kurath, D. E. *Technetium in alkaline, high-salt, radioactive tank waste supernate: preliminary characterization and removal*; PNL Report PNL-11386, January 1997. (e) Bray, L. A.; Amonette, J. E.; Brown, G. N.; Kafka, T. M.; Yates, S. F. *Efficient separations and processing crosscutting program: develop and test sorbents*; PNL Report PNL-10750, September 1995.

(11) Allen, F. H.; Kennard, O. *Chem. Design Autom. News* **1993**, *8*, 31.

(12) (a) Hay, B. P. *Coord. Chem. Rev*. **1993**, *93*, 77. (b) Landis, C. R.; Root, D. M.; Cleveland, T. *Rev. Comput. Chem*. **1995**, *6*, 73. (c) Cundari, T. R. *J. Chem. Soc., Dalton Trans*. **1998**, 2771.

(13) Cundari, T. R.; Deng, J. *J. Chem. Inf. Comput. Sci*. **1999**, *39*, 376 and references therein.

(14) Cundari, T. R.; Fu, W. *Inorg. Chem. Acta* **2000**, *300−302*, 113.

(15) Cundari, T. R.; Deng, J.; Fu, W. *Int. J. Quantum Chem*. **2000**, *77*, 421.

the novel LIGB scheme in Macromodel,[17] which is described later. The second CS protocol involved high-temperature (750 K) molecular dynamics/simulated annealing (MD/SA) with the HyperChem software:[18] 0.5 ps heating, 1.0 ps equilibration, 0.5 cooling, 2 fs time steps. The geometries thus obtained (in general the number of MD/SA cycles is 10−20 times the number of atoms) were then geometry optimized with MM. Structures were considered to be duplicate if their energies agreed to within 0.001 kcal/mol.

Structures obtained from both CS techniques were first evaluated in single-point PM3(tm)-GA calculations at the MM geometries in order to determine the appropriate spin state. Subsequent PM3(tm)-GA geometry optimizations were carried out at the spin state predicted by this semiempirical method to be the lowest in energy. Other research in our lab indicates that PM3(tm)-GA yields the same predicted ground-state multiplicities as more expensive density functional theory calculations.[19]

The solid-state structures of all the target species are available in the Cambridge Structural Database (CSD).[11] A variety of complex types were chosen to test the performance envelope of the MM−SEQM search protocol. However, in all cases, the initial geometries were sketched in using the appropriate graphical user interfaces provided with each program *without* utilizing or referring to the X-ray crystal structure for guidance.

This research employed the Titan,[20] HyperChem,[18] and Macromodel[17] packages.

## Results and Discussion

**1. LIGB Conformational Searching Technique.** The LIGB (LIGand Bond) method is an extension of the MCMM (Monte Carlo multiple minimum) conformational search method[21] long available in the MacroModel molecular modeling package.[17] In the MCMM method, a gross random change is made to the molecular geometry, and the resulting structure is minimized. The minimized structure is accepted if it is unique among those found at that point in the search and if its energy is below a specified threshold with respect to the global minimum found thus far. Following acceptance or rejection, a random saved conformation is selected and resubjected to the basic cycle of distortion and minimization. Each such cycle constitutes a search step, and the user specifies how many steps are to be carried out. The search is usually deemed complete when all low-energy conformations have been found multiple times.

In the MCMM method as originally implemented, two types of geometric distortion are utilized: a random set of rotatable bonds is rotated by random values (with appropriate ring openings if any of the selected torsions are in rings), or if the system under study is a complex of several molecules, a random subset of these molecules is translated and rotated by random amounts. LIGB augments MCMM with a third type of distortion. The user designates a list of bonds as ligand bonds. In an LIGB "move", these bonds are first broken; then, the detached fragments formed by the bond breaking are each subjected to random translation and rotation as if they were independent molecules. Then, the bonds are reformed prior to minimization.

Even when applied to organic structures, this procedure enables structural changes that are not possible without LIGB. For example, if the bonds to a tetrahedral stereogenic center are designated LIGB bonds, an MCMM search will allow inversion of chirality. If there are several stereogenic centers present, applying LIGB to all of them will allow all diastereomers to be explored from a single starting structure. However, if the user does not wish to convert between stereoisomers, this feature can be turned off. For example, we would expect strain energy to be the most important determinant of the distribution of diastereomers present after incubation of a system under conditions allowing thermal equilibration. An LIGB search on such a system would allow all diastereomers to be found and their strain-energy differences to be computed.

In the study of transition metal complexes, the use of LIGB is not as straightforward as in the case of organic systems. The problem with modeling inorganic complexes lies chiefly in the definition of the bond angle terms in the force field. Consider, for example, the *cis* and *trans* isomers of the octahedral complex $MA_2B_4$. The A−M−A bond angle has the equilibrium value of 90° in the *cis* form and 180° in the *trans* form. MacroModel has facilities to treat such systems if provided with near-equilibrium geometries: the force-field files may encode geometry-dependent parameters that say, in effect, "If the A−M−A bond angle starts out close to 90°, make its equilibrium value 90°; otherwise, make it 180°". Three-way decisions can be encoded for trigonal-bipyramidal complexes and so on. However, this paradigm does not work for the highly distorted structures created by the LIGB command. In an octahedral complex, there are 15 bond angles about the metal. Three of them have equilibrium values of 180°, and the rest have equilibrium values of 90°. Imagine an LIGB distortion that creates a nearly linear $MA_2B_4$ system. Because none of the X−M−Y bond angles will be close to 90° prior to minimization, all bond angles will get equilibrium values of 180°. Minimizing this structure will certainly not give the desired octahedral geometry. Though LIGB creation of a linear system is improbable, the creation of a distorted structure with just the right geometry to minimize to an octahedral complex is also improbable.

For this reason, the LIGB method is used with the VDWB (van der Waals bends) command when coordination numbers above four are studied. VDWB redefines the potential energy surface and thus affects conformational search indirectly. The user designates a list of bond angle interactions as VDWB. Then, rather than being modeled using the force field's bond angle potential, a repulsive term is applied between the terminal atoms of the bond angle triplet. Thus, in an

(16) Benson, M. T.; Cundari, T. R.; Lutz, M. L.; Sommerer, S. O. Effective Core Potential Approaches to the Chemistry of the Heavier Elements. In *Reviews in Computational Chemistry*; VCH: New York, 1996, Vol. 8, pp 145−202. (b) Frenking, G.; Antes, I.; Bohme, M.; Dapprich, S.; Ehlers, A. W.; Jonas, V.; Neuhaus, A.; Otto, M.; Stegmann, R.; Veldkamp, A.; Vyboishchikov, S. F. Pseudopotential Calculations of Transition Metal Compounds: Scope and Limitations. In *Reviews in Computational Chemistry*; VCH: New York: 1996, Vol. 8, pp 63−144.
(17) *Macromodel*; Schrödinger, Inc.: Portland, OR, http://www.schrodinger.com/Products/macromodel.html.
(18) *HyperChem*; HyperCube, Inc.: Gainesville, FL, http://www.hyper.com.
(19) Ball, D. M.; Buda, C.; Cundari, T. R.; Gillespie, A.; White, D. P. *Inorg. Chem.* **2002**, *41*, 152.
(20) *Titan*; Schrödinger, Inc.: Portland, OR, http://www.schrodinger.com/Products/titan.html.
(21) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

octahedral complex, all X−M−Y bond angle terms would be replaced by 1,3 X···Y van der Waals repulsions. Note that the M−X stretch interactions are still present and allowed to vary. The net effect of this is that the system is modeled using a points-on-a-sphere model.[12,14]

**2. Predictive Capacity of Standard and Genetic Algorithm Optimized PM3(tm).** One of the major advantages of SEQM versus MM methods is the limited parametrization investment that is required for the former. For a single TM, it is only necessary to develop 21 PM3(tm) parameters. Then, it is possible to model all complexes of this TM with PM3(tm) assuming the ligands contain no further unparametrized atoms. For MM force fields, the number of optimizable parameters can easily be double or treble that for SEQM for a reasonable assortment of new ligating atom types. Our initial research on PM3(tm)-GA was motivated by the desire to assess the performance of GAs for optimization problems of this type and the unavailability of any Tc PM3(tm) parameters at that time. Subsequently, a Tc PM3(tm) parametrization has been made available, and it is of interest to compare its performance with the GA-optimized, PM3(tm) parameters previously reported.[15]

For these purposes, 197 Tc complexes were selected from the Cambridge Structural Database.[11] Complexes extracted were limited to those that had their 3D coordinates deposited, *R* (residual) values < 10%, were not disordered, had no detected crystallographic errors, and were not polymeric. PM3(tm) and PM3(tm)-GA geometry optimizations were performed for all 197 Tc compounds starting each with the X-ray coordinates. The results in terms of predictive ability of Tc−ligand bond lengths and ligand−Tc−ligand bond angles were assessed by comparison with experiment. The majority of these compounds (160 out of 197) contained one Tc atom, 32 have 2 Tc atoms, 1 has 3 Tc atoms, and 4 have 4 Tc atoms. The preponderance of the compounds contained 6-coordinate Tc (110) and 5-coordinate Tc (65). The other compounds contained 7-coordinate Tc (14), 4-coordinate Tc (6), and polymetallic complexes in which the Tc atoms have different coordination number (2). These compounds have the following ligand donor atoms: sp3 amine N, sp2 imine N, enolate O, oxo O, phosphine P, chloride Cl, carboxylate O, sp2 amide N, thiolate S, and thiol S. The complete list of target complexes is available as Supporting Information.

The results of the standard PM3(tm) parametrization and the GA-optimized PM3(tm) parameters are summarized in Table 1. In comparison with PM3(tm), PM3(tm)-GA provided better predictive ability for 138 out of 197 (70%) structures across the entire target set and 120 out of 160 (75%) for compounds with a single Tc atom. The performance of both parametrizations was essentially equal for poly-Tc complexes: 18 out of 37 (49%) compounds with more than 1 Tc atom showed better predictive ability with PM3(tm)-GA. For the entire series of 197 complexes, the average absolute percent difference (Δ%) between computed and X-ray structures in Tc-dependent bond lengths and angles was 7.9% (PM3(tm) and 4.4% (PM3(tm)-GA); the median Δ% for the entire dataset was 4.9% (PM3(tm)) and 3.5% (PM3(tm)-GA), indicating the former is more prone to very large errors in prediction. For the two dominant coordination numbers, PM3(tm)-GA outperformed the standard PM3(tm) parametrization in 46 out of 65 (71%) cases for 5-coordinate Tc and 85 out of 110 (77%) cases for 6-coordinate Tc. The standard parametrization is clearly better for 7-coordinate Tc complexes; in 3 out of 14 (21%), PM3(tm)-GA outperformed PM3(tm). The results indicate that for the most prevalent Tc structural motifs significant improvement in structural predictive ability can be obtained using a GA optimization scheme for SEQM parameters.

**Table 1.** Comparison of PM3(tm) and PM3(tm)-GA Calculations[a]

| criteria | types | params | "better" | av Δ% | med Δ% | min Δ% | max Δ% |
|---|---|---|---|---|---|---|---|
| Tc complexes | all (197) | PM3(tm) | 59 | 7.9 | 4.9 | 0.9 | 58.8 |
| | | PM3(tm)-GA | 138 | 4.4 | 3.5 | 0.8 | 19.3 |
| number of Tc atoms | 1 (160) | PM3(tm) | 40 | 7.6 | 5.1 | 0.9 | 58.8 |
| | | PM3(tm)-GA | 120 | 4.2 | 3.5 | 0.8 | 19.3 |
| | 2;3;4 (37) | PM3(tm) | 19 | 9.5 | 4.5 | 1.5 | 40.4 |
| | | PM3(tm)-GA | 18 | 4.9 | 3.7 | 1.4 | 16.3 |
| coordination number | 4 (6) | PM3(tm) | 3 | 4.0 | 3.6 | 2.3 | 7.9 |
| | | PM3(tm)-GA | 3 | 2.8 | 2.7 | 2.2 | 3.5 |
| | 5 (65) | PM3(tm) | 19 | 4.0 | 4.1 | 0.9 | 9.1 |
| | | PM3(tm)-GA | 46 | 3.2 | 2.8 | 0.8 | 6.1 |
| | 6 (110) | PM3(tm) | 25 | 10.3 | 7.9 | 1.2 | 58.8 |
| | | PM3(tm)-GA | 85 | 4.9 | 4.0 | 1.5 | 19.3 |
| | 7 (14) | PM3(tm) | 11 | 7.1 | 3.1 | 1.5 | 23.8 |
| | | PM3(tm)-GA | 3 | 6.0 | 4.5 | 2.0 | 13.8 |

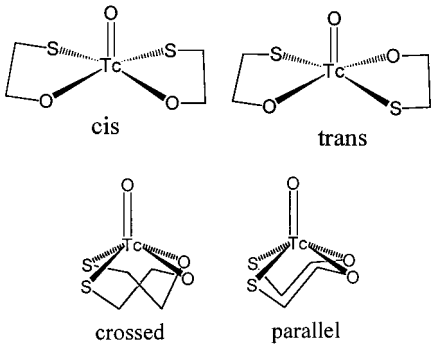
**3. *De Novo* Structural Prediction of Technetium Complexes.** On the basis of our research, both conformational searching schemes (LIGB and high-temperature-MD/SA) permit one to probe not only conformational isomerism as in a typical application to organic species, but also geometric isomerism (e.g., *cis* and *trans* or *fac* and *mer* octahedral complexes), which in most cases is more crucial for a TM complex. Furthermore, LIGB and MD/SA both perform similarly in terms of finding the same low-energy geometries, although the LIGB approach is superior for macrocyclic complexes. Given the similarity of the CS results, and the superiority of LIGB for macrocycles, the discussion below for specific molecules will focus on the predictive results obtained with LIBG conformational searching.

**a. *ASMETE* (Bis(2-mercaptoethanolato)-oxo-technetium(V) Anion).**[22] Of the five lowest energy isomers (which are within 0.2 kcal/mol) obtained from the LIGB search, four possess the expected apical-oxo arrangement. The remaining structure, which is the fourth lowest in energy, has the oxo in a basal coordination site of the square pyramid. The four apical-oxo geometries differ in that the sulfur atoms of the 2-mercaptoethanolato ligand are *cis* or *trans*, while the ethylene functionalities of each ligand have approximate $C_2$ (crossed) or $C_s$ (parallel) local symmetry.

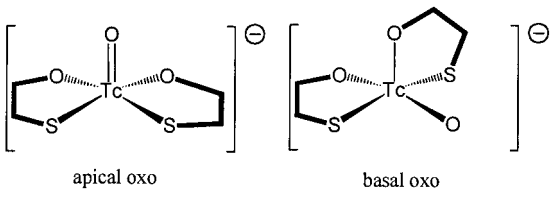
Submission of the low-energy conformations obtained from the MM search to PM3(tm)-GA optimization (singlet spin state) shows a preference for a *cis* arrangement of the 2-mercaptoethanolato ligands by >5 kcal/mol over the *trans*. The *cis* geometry is consistent with the X-ray structure of *ASMETE*.[22] Among the *cis* structures, the crossed ethylene arrangement, which is the one found in the X-ray structure,

(22) *ASMETE*: Jones, A. G.; DePamphilis, B. V.; Davison, A. *Inorg. Chem.* **1981**, *20*, 1617.

is lower by 1 kcal/mol than the parallel conformation. Hence, the combined MM−SEQM protocol predicts the correct structure.



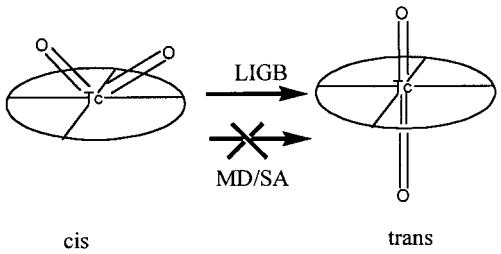

This simple structure shows one of the major advantages of coupling steric (MM) and electronic (SEQM) methods within a single, fast *de novo* scheme for TM complexes. While both the apical and basal oxo geometries are sterically reasonable, the latter is clearly untenable from an electronic point of view. Inspection of the CSD reveals numerous examples of five-coordinate TM-oxos, all of which possess the apical-oxo structure.



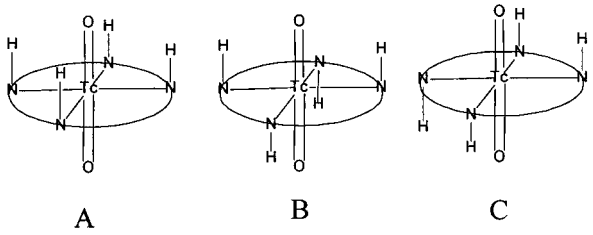

**b. *BAJDOF* (Dichloro-bis(bis(1,2-dimethylphosphino)-ethane)-technetium(III) Cation).**[23] Conformational searching of this complex yields 8 unique conformations. These conformations distribute themselves within two classes, *cis* and *trans*. Sterically, the *trans* structures are predicted to be lower in energy than the *cis*; the lowest energy *trans* conformation is 3 kcal/mol more stable than the lowest energy *trans* conformer.

Given an octahedral geometry for $d^4$-Tc(III), singlet, triplet, or quintet spin states are possible. Single point PM3(tm)-GA calculations utilizing an unrestricted wave function at the MM geometries suggests the following energetic ordering: triplet < singlet ≪ quintet. Hence, PM3(tm)-GA geometry optimizations were performed on the triplet state of $[TcCl_2(dmpe)^2]^+$. The *trans*-dichloro isomers are predicted to be more stable by ≈18 kcal/mol, consistent with the X-ray structure *BAJDOF*.[23] The ethylene spacers of the dmpe ligands are parallel in the X-ray structure, while the PM3(tm)-GA optimizations predict the crossed conformation to be lower in energy, although the difference in energy is <0.2 kcal/mol. Hence, in this instance, the MM and SEQM predictions reinforce each other.

**c. *BAPPIR* (*trans*-Dioxo-(1,4,8,11-tetra-azacyclotetradecane)-technetium(V) Cation).**[24] This complex is a particularly good test of conformational searching protocols for metal complexes given the myriad of conformations possible for 1,4,8,11-tetra-azacyclotetradecane. Macrocycles, furthermore, compose the one class of complexes in which LIGB is notably superior to the high-temperature MD/SA conformational searching scheme. The latter does not, given a *cis* starting geometry, yield any *trans* geometric isomers. This is most likely due to the enormous energy barriers for *cis* to *trans* conversion. Tests with extremely high temperature (>1000 K) molecular dynamics either do not rectify this situation or lead to unstable simulations that dissociate the molecule. This is not the case for the related, nonmacrocyclic complex (*NIPRIN*, vide infra) in which both methods generate and search *cis* and *trans* dioxo geometries. Low-energy *BAPPIR*




conformations are primarily discriminated, in an energetic sense, by the relative orientation of the amine protons. The lowest energy steric conformations are depicted here, **A**−**C**.

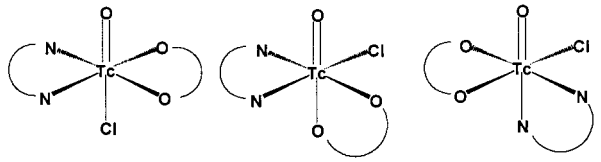



For PM3(tm)-GA geometry optimizations, attention was focused on *trans*-dioxo conformations obtained from the LIGB search as analysis of the CSD shows this arrangement to be preferred for $d^2$-dioxos. Additionally, other tests for *NIPRIN* (vide infra) show that PM3(tm)-GA optimization of *cis*-Tc(V)-dioxo structures results in rearrangement back to the *trans* geometry or dissociation of an amine, both of which are much higher in energy than the *trans* structures. PM3(tm)-GA optimization of [*trans*-dioxo-(1,4,8,11-tetra-azacyclotetradecane)-technetium(V)]$^+$ (singlet spin state) shows conformations such as **C** with *cis* pairs of amine protons on the same side of the macrocycle ring ($C^2$ symmetry) to be lower than any other conformation by >3 kcal/mol. The predicted conformation from the combined MM−SEQM search is thus consistent with the experimental structure of *BAPPIR* in all respects.[24]

(23) *BAJDOF10*: Vanderheyden, J. L.; Ketring, A. R.; Libson, K.; Heeg, M. J.; Roecker, L.; Motz, P.; Whittle, R.; Elder, R. C.; Deutsch, E. *Inorg. Chem.* **1984**, *23*, 3184.

(24) *BAPPIR*: Zuckman, S. A.; Freeman, G. M.; Troutner, D. E.; Volkert, W. A.; Holmes, R. A.; VanDerveer, D. G.; Barefield, E. K. *Inorg. Chem.* **1981**, *20*, 2386.

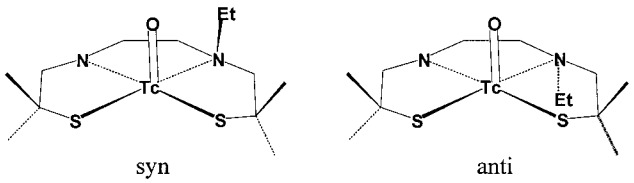
**d. *GELFAE* (Chloro-(1,2-ethanediolato)-oxo-(1,10-phenanthroline-*N*,*N*′)-technetium(V)).**[25] For this complex, three groups of conformational isomers (**D**−**F**) are expected and found from the MM conformational search. The MM force field yields the following energetics ordering: **F** < **D** < **E**. Submission of these structures to further refinement by PM3(tm)-GA geometry optimization (singlet spin state) indicates that geometry **F** is the electronically preferred one, consistent with the X-ray crystallographic evidence for ***GELFAE***.[25] The SEQM-derived energy ordering of the geometric isomers is the same as that of the MM: **F** < **D** (by 4 kcal/mol) < **E** (14 kcal/mol above isomer **F**).




D E F

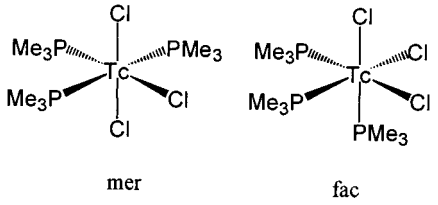
**e. *JEVMAY* (*mer*-Trichloro-tris(4-picolinato)-technetium(III)).**[26] The 4-Me groups of the picoline ligands in *JEVMAY* were modeled as pyridine (py) because it was assumed this substitution would not affect the outcome. Conformational searching of $TcCl_3(py)_3$ was begun from the *fac* geometry. This search yielded two geometries: *fac* and *mer*. The *mer* isomer is predicted by the MM force field to be lower by 2 kcal/mol than the *fac* isomer. PM3(tm)-GA calculations at the MM geometries utilizing an unrestricted wave function point to a quintet ground state. Geometry optimization at this spin state indicates that the ground state is the *mer* isomer, which is in agreement with the solid-state geometry of *JEVMAY*.[26]

**f. *JIDLOX* (*syn*-(4-Et-2,9-dimethyl-4,7-diaza-2,9-decanedithiolato)-oxo-technetium(V)).**[27] This complex is of interest since it has been studied in connection with its use for medical imaging.[5] Furthermore, it possesses the $N_2S_2$ ligating atom motif that is prevalent in Tc radiochemistry, particularly for renal imaging agents. The main challenge in modeling *JIDLOX* lies in the correct prediction of the relative orientation of the oxo and the ethyl group bonded to the coordinated amine ligand, *syn* or *anti*. On a steric (by >1 kcal/mol) and electronic (>2 kcal/mol) basis the syn conformation is preferred as is found in the X-ray structure of *JIDLOX*.[27]




syn anti

**g. *KOMNEF* (*mer*-Trichloro-tris(triphenylphosphine)-technetium(III)).**[28] As with *JEVMAY*, this complex tests the ability of the LIGB and MD/SA techniques to find *fac* and *mer* isomers for an octahedral-$MA_3B_3$ complex. Indeed, searches were begun from both *fac* and *mer* (X-ray) isomers of $TcCl_3(PMe_3)_3$, and the same conformations found regardless of the geometry used to initiate the conformational search. MM predicts the *fac* to be substantially preferred, being >2 kcal/mol lower in energy than the most stable *mer* conformation.




After taking these lowest energy *fac* and *mer* structures obtained from MM and performing single-point PM3(tm)-GA calculations, a quintet ground state is indicated. Geometry optimization of quintet *fac*- and *mer*-$TcCl_3(PMe_3)_3$ reverses the steric preference for the former. The *mer* isomer is 27 kcal/mol lower in energy than the PM3(tm)-optimized *fac* isomer. This prediction is supported by the X-ray structure of *KOMNEF*[28] and the greater preponderance of *mer*-$MCl_3(PR_3)_3$ structures in the CSD: 11 are *mer*, and 1 is *fac*.

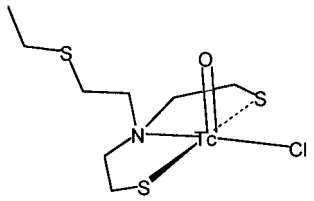
In this complex, as in others (e.g., *cis*- versus *trans*-dioxos), it is seen that a strength of a combined MM−SEQM protocol is the ability to provide electronic discrimination in cases where the MM force field is either unable to predict or predicts steric energies that are clearly within the error limits of the method.

**h. *LALGUA* (*trans*-Tetrachloro-bis(trimethylphosphine)-technetium(IV)).**[29] Conformational searching yields cis and trans geometries for $TcCl_4(PMe_3)_3$. The MM force field predicts the *cis* geometry to be lower by 0.5 kcal/mol. PM3(tm)-GA geometry optimization of both geometric isomers (quartet spin state) reverses the steric prediction and yields a *trans* isomer that is lower by 7 kcal/mol than *cis*-$TcCl_4(PMe_3)_3$, a result consistent with the X-ray geometry of *LALGUA*.[29]

**i. *LIGKIV* (Chloro-(*N*,*N*-bis(2-mercaptoethyl)-2-(ethylthio)ethylamine-*N*,*S*,*S*′)-oxo-technetium(V)).**[30] This complex is a structural motif of interest in connection with Tc-RPCs.[5] Derivatives of *LIGKIV* with pendant groups other than 2-(ethylthio)ethylamine have been tested for medical imaging. The primary conformational complexity of this complex arises from the "floppy" 2-(ethylthio)ethylamine moiety; from a search of 1000 complexes,[27] conformations

(25) *GELFAE*: Pearlstein, R. M.; Lock, C. J. L.; Faggiani, R.; Costello, C. E.; Zeng, C. H.; Jones, A. G.; Davison, A. *Inorg. Chem.* **1988**, *27*, 2409.
(26) *JEVMAY*: Lu, J.; Yamano, A.; Clarke, M. J. *Inorg. Chem.* **1990**, *29*, 3483.
(27) *JIDLOX*: Mahmood, A.; Halpin, W. A.; Baidoo, K. E.; Sweigart, D. A.; Lever, S. Z. *Acta Crystallogr. C* **1991**, *47*, 254.
(28) *KOMNEF*: Watson, P. L.; Albanese, J. A.; Calabrese, J. C.; Ovenall, D. W.; Smith, R. G. *Inorg. Chem.* **1991**, *30*, 4638.
(29) *LALGUA*: Rochon, F. D.; Melanson, R. *Acta Crystallogr. C* **1993**, *49*, 1259.
(30) *LIGKIV*: Mastrostamatis, S. G.; Papadopoulos, M. S.; Pirmettis, I. C.; Paschali, E.; Varvarigou, A. D.; Stassinopoulou, C. I.; Raptopoulou, C. P.; Terzis A.; Chiotellis, E. *J. Med. Chem.* **1994**, *37*, 3212.

that are within 1 kcal/mol of the lowest energy conformation are found.

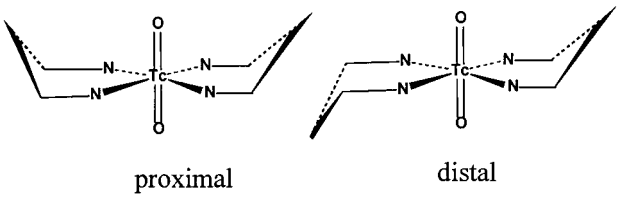



As with *JIDLOX*, the primary steric energetic discriminator among the different geometries is the orientation of the amine pendant group *syn* or *anti* to the oxo oxygen. The preference for the *syn* arrangement is small at the MM level (0.2 kcal/mol) but more substantial upon incorporation of electronic effects ($\Delta\Delta H_f$(PM3)*anti*−*syn* = 2.2 kcal/mol). The crystal structure of *LIGKIV* has a *syn* oxo-pendant group geometry,[30] in agreement with the MM−SEQM calculations. The only major structural discrepancy between the crystal structure geometry and the PM3(tm)-GA calculated geometry lies in the dihedral angles of the pendant $CH_2CH_2SCH_2CH_3$ group. It is reasonable to presume that in solution the molecule will sample a large ensemble of pendant group conformations. The conformer most similar to the crystal conformation is 0.6 kcal/mol above the lowest energy conformation predicted by PM3(tm)-GA.

**j. *NIPRIN* (Bis(trimethylenediamine)-dioxo-technetium(III) cation).**[31] The $d^2$-dioxo complex *NIPRIN* is, in many respects, similar to the macrocycle *BAPPIR* discussed previously. The main distinction lies in the different flexibility of the chelating trimethylenediamine (pn) versus the macrocylic 1,4,8,11-tetra-azacyclotetradecane.

Conformational searching of $[Tc(O)_2(pn)_2]^+$ yields 10 low energy structures. Both *cis* and *trans* dioxo geometric isomers are found, as well as those in which either or both of the Tc−pn six-membered rings possess a chair or twist boat conformation. The MM conformational search correctly discriminates boat and chair Tc−pn geometries (boat < chair by approximately 10 kcal/mol) but predicts the lowest energy geometry to be a *cis*-dioxo.

PM3(tm)-GA optimization of all four geometries found by the LIGB search, *cis* or *trans* dioxo, with boat Tc-pn conformations (singlet spin state) results in a clear energetic (>14 kcal/mol) preference for the *trans*-$d^2$-Tc(V)-dioxo geometric isomer. The two lowest energy conformations differ in the relative orientation of the Tc−pn boats: proximal or distal. The distal conformation, which is that of the crystal *NIPRIN*,[31] is predicted to be lower in energy at the PM3(tm)-GA level of theory, albeit by only 0.1 kcal/mol relative to the proximal geometry.




**k. *PAQWEJ* (*trans,cis,cis*-Dioxo-dipyridyl-bis(trimethylphosphino)-technetium(V) Cation).**[32] There are five isomers for an octahedral $MA_2B_2C_2$ complex. One of them in which the corresponding groups are all mutually *trans* (ttt), another in which they are all *cis* (ccc), and three in which one of the ligand pairs is *trans* while the remaining two are *cis* (tcc, ctc, and cct). The LIGB conformational search finds all five conformations. Upon PM3(tm)-GA optimization of the five MM-derived geometries, it is found that the most stable geometry is *trans,cis,cis*-$[TcO_2py_2(PMe_3)]_2]^+$, 2 kcal/mol lower in energy than *trans,trans,trans*-$[TcO_2py_2(PMe_3)]_2]^+$. The X-ray structure of *PAQWEJ*[32] is thus consistent with MM−SEQM prediction.

**l. *PCLTCA* (1-Oxo-2,3,6-(D-penicillaminato-*N,S,O*)-4,5-(D-penicillaminato-*N,S*)-technetium(V)).**[33] This complex embodies the chemical diversity of transition metal complexes, in general, and technetium, in particular. Within a single complex, Tc is coordinated to soft sulfur donors as well as hard oxygen and nitrogen donor ligands. Bond types are multiple (Tc−oxo), single (Tc−thiolate and Tc−carboxylate), and dative (Tc−amine) in 1-oxo-2,3,6-(D-penicillaminato-*N,S,O*)-4,5-(D-penicillaminato-*N,S*)-technetium(V).

Working from the reasonable assumption that the tridentate D-penicillaminato-*N,S,O* will assume a *fac* coordination mode about Tc, while the bidentate D-penicillaminato-*N,S* must ligate in a *cis* fashion, there are six families of geometric isomers, labeled α, $\beta$, $\gamma$, $\delta$, $\epsilon$, and $\phi$.

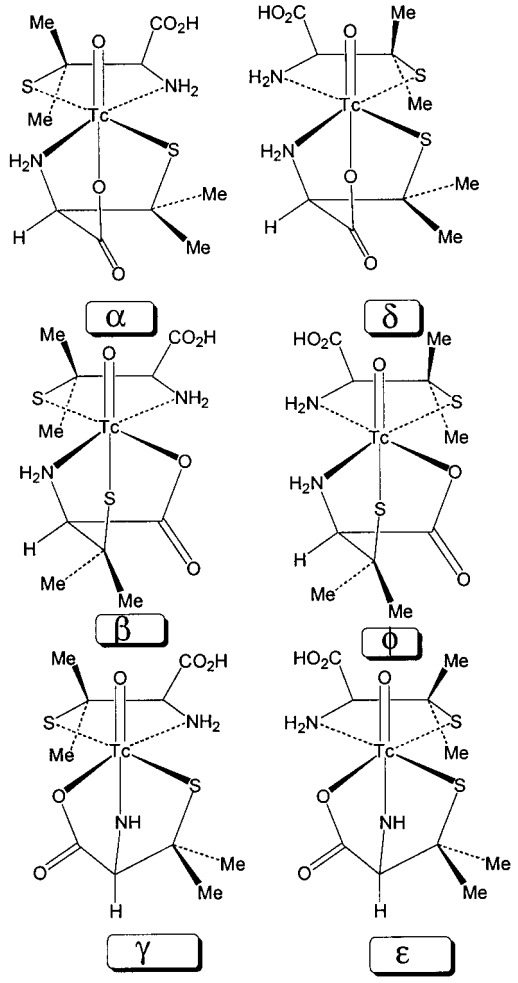
The LIGB search finds only five of the six ideal geometric isomers described here. Isomer $\phi$ is observed neither with 1,000 geometries generated nor with 5,000 geometries in the LIGB conformational search. It was found by manually building isomer $\phi$ that it undergoes a reorganization to isomer α. Hence, it is possible that isomer $\phi$ is either a high energy structure that lies outside the 50 kJ/mol window for "accepted" structures in LIGB or that it does not represent a local minimum.

Within each geometric isomer manifold, a variety of conformational isomers is possible. To simplify the search, the lowest conformation (which differs primarily because of the carboxylic acid group) obtained from the MM-based LIGB search was submitted to PM3(tm)-GA geometry optimization (singlet spin state). Isomer $\delta$ is substantially more stable, being 6 kcal/mol below the next lowest energy isomers (α and $\epsilon$). Manually constructing isomer $\phi$ and submitting it to PM3(tm)-GA optimization results in a structure that is 14 kcal/mol higher than the lowest energy isomer found. The energy ordering derived from the PM3(tm)-GA geometries is as follows: $\delta < \alpha = \epsilon < \gamma < \beta < \phi$.

The experimental geometry differs from the geometry arrived at through the MM−SEQM protocol primarily in the disposition of the $CMe_2$ group α to the thiolate S. An optimization starting from the crystal geometry[33] yields a

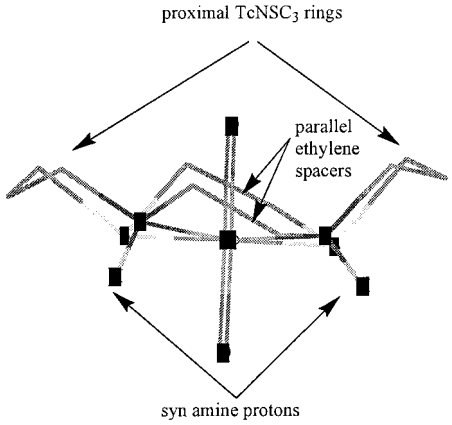
(31) *NIPRIN*: Kremer, C.; Gancheff, J.; Kremer, E.; Mombru, A. W.; Gonzalez, O.; Mariezcurrena, R.; Suescun, L.; Cubas, M. L.; Ventura, O. N. *Polyhedron* **1997**, *16*, 3311.
(32) *PAQWEJ*: Rochon, F. D.; Melanson, R.; Kong, P. C. *Inorg. Chem.* **1998**, *37*, 87.
(33) *PCLTCA10*: Franklin, K. J.; Howard-Lock, H. E.; Lock, C. J. L. *Inorg. Chem.* **1982**, *21*, 1941.

PM3(tm)-GA stationary point that is only 1 kcal/mol *lower* in energy than the lowest energy conformation found from the MM−SEQM search.

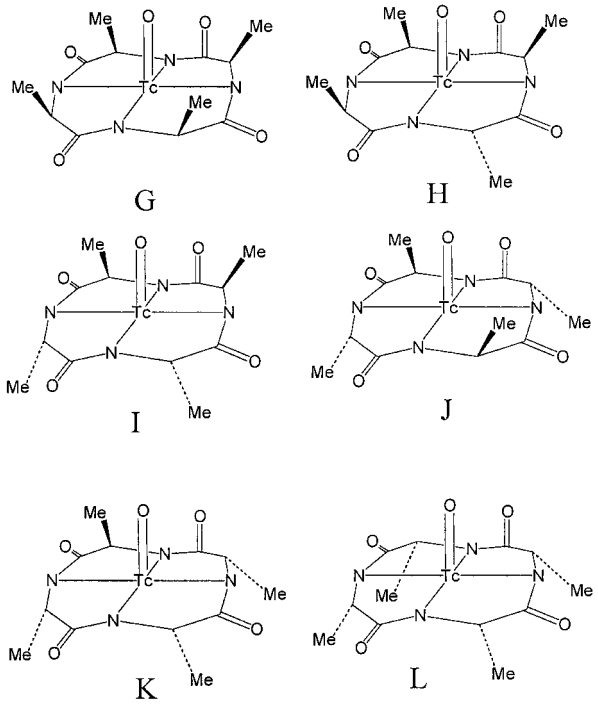



**m. *SAJTIG* (*trans*-Dioxo-(1,4-dithia-8,11-diazacyclotetradecane-*N*,*N*′,*S*,*S*′)-technetium(V) Cation).**[34] Taking the *trans*-dioxo arrangement as a given (although both *cis* and *trans* geometries were explored), the conformations of this six-coordinate macrocycle differ primarily because of the relative orientation of amine protons (pointing toward the same or different side of the macrocycle ring), the pucker of the six-membered $TcNSC_3$ rings (proximal and distal akin to *NIPRIN*), and the relative orientation of the ethylene spacers (crossed or parallel).

The LIGB search protocol resulted in several dozen distinct conformations; taking the 10 lowest *trans*-dioxo geometries thus obtained (which span a range of 12 kcal/mol) and submitting them to PM3(tm)-GA geometry optimizations (singlet spin state) leads to the prediction that the lowest energy geometry has *syn* amine protons, a proximal pucker to the $TcNSC_3$ rings, and a parallel arrangement of the ethylene spacers. This geometry is favored by almost 1 kcal/mol versus the next lowest conformation and is consistent with the X-ray geometry[34] in all respects.




**n. *TOXMEY* ((Cyclo-tetra-L-alanyl)-oxo-technetium(V) Anion).**[35] Given the planarity of the amide NC(═O) functionalities, geometries arise from the disposition of the L-alanyl methyl groups relative to the oxo. This LIGB search, as with all others, was not limited by the need to preserve the handedness of stereogenic centers. Visual inspection of the complex suggests that there should be six conformations if one assumes (and indeed finds) that the Tc═O moiety occupies the apical site of a square pyramid: (*syn*-Me),[4] **G**; (*syn*-Me)$_3$(*anti*-Me), **H**; *cis*-(*syn*-Me)$_2$(*anti*-Me)$_2$, **I**; *trans*-(*syn*-Me)(*anti*-Me)$_2$, **J**; (*syn*-Me)(*anti*-Me)$_3$, **K**;. and (*anti*-Me)$_4$, **L**.



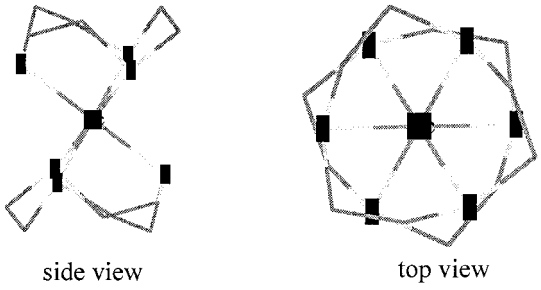

An initial LIGB search of 1000 geometries did not find all six of these low energy, *trans*-dioxo conformations. Hence, a more extensive search of 5000 geometries was

(34) *SAJTIG*: Ianoz, E.; Mantegazzi, D.; Lerch, P.; Nicolo, F.; Chapuis, G. *Inorg. Chim. Acta* **1989**, *156*, 235.

(35) *TOXMEY*: Bormans, G.; Peeters, O. M.; Vanbilloen, H.; Blaton, N.; Verbruggen, A. *Inorg. Chem.* **1996**, *35*, 6240.

performed, which yielded all six *TOXMEY* conformations. Geometry optimization of the six conformations of [(cyclotetra-L-alanyl)-oxo-technetium(V)]$^-$ using the PM3(tm)-GA Hamiltonian leads to the prediction that the lowest energy conformation by 2 kcal/mol is that in which all L-alanyl Me groups are *syn* to the oxo oxygens as observed in the experimental structure.[35] The energy of the *TOXMEY* conformations rises monotonically for each Me group that is moved from a *syn* to *anti* conformation.

**o. *WACXIH* (Bis(1,4,7-trithiacyclononane-*S*,*S*′,*S*″)-technetium(II) Dication).**[36] Six unique conformations spanning 12 kcal/mol were found by the LIGB conformational search. After determination of a preference for the low-spin doublet multiplicity from single-point PM3(tm)-GA calculations, SEQM geometry optimization was performed. The lowest energy geometry thus obtained has near $S_6$ symmetry and is identical to that conformation obtained when starting with the crystal structure geometry[36] of *WACXIH* and submitting it directly to PM3(tm)-GA for geometry optimization.




**p. *ZOPWAC* (Dichloro-tetrapyridyl-technetium(II)).**[37] Two conformations of $TcCl_2py_4$ are obtained, *cis* and *trans*. The MM force field predicts the *trans* to be more stable than the *cis* by 2 kcal/mol. Single-point PM3(tm)-GA calculations at the MM geometries (sextet spin state) indicates that the *trans* isomer lies 20 kcal/mol below the *cis* isomer. PM3(tm)-GA geometry optimization from these MM starting points (sextet spin state) results in dissociation of the pyridine for the *cis* isomer, resulting in only a stable *trans*-$TcCl_2py_4$ geometry. The solid-state structure of *ZOPWAC* is *trans*-dichloro.[37]

**q. Trigonal Prismatic Technetium Complexes.** The complex *BUMCER* (tris(2-aminobenzenethiolato-*S*,*N*)-technetium(VI))[38] is a very interesting test of an integrated MM−SEQM *de novo* structural prediction protocol because it is one of only two six-coordinate Tc complexes in the CSD with a *trigonal prismatic* coordination geometry. Not surprisingly, the MM-based, LIGB conformational search arrives at two *octahedral* geometries, corresponding to *fac* and *mer* arrangements of the three thiolato ligands. Upon PM3(tm)-GA optimization of these MM starting geometries (doublet spin state), two distinct structures are obtained, a high energy, *mer* octahedral complex, and a trigonal prismatic structure that is 15 kcal/mol lower in energy. The trigonal prismatic structure obtained from the MM−SEQM search is identical to that obtained from a PM3(tm)-GA optimization starting from the X-ray coordinates of *BUMCER*.

There is another trigonal prismatic Tc complex, *FOPBER* (tris(benzene-1,2-dithiolato-*S*,*S*′)-technetium(V) anion),[39] in the CSD. This tris(dithiocatecholate) complex yields only a single, octahedral geometry from the LIGB search, as expected. PM3(tm)-GA geometry optimization (singlet spin state) of the octahedral MM geometry yields a trigonal prismatic structure consistent with the crystal geometry. It must also be noted that a related complex *VATTOZ* (tris-(3,5-di-*tert*-butylcatecholato-*O*,*O*′)-technetium(VI))[40] has a geometry that is closer to octahedral than trigonal prismatic but is predicted to be trigonal prismatic (doublet spin state) at the PM3(tm)-GA level of theory. Hence, it is likely that the energetic balance between octahedral and trigonal prismatic forms is quite close for some Tc tris(catecholate) congeners.

## Summary

The results of this research, for a wide variety of technetium complexes, demonstrate several important conclusions with respect to the development of efficient and effective computational schemes for *de novo* structural prediction of transition metal complexes.

(1) A new conformational searching algorithm (LIGB) has been described. This technique now allows the inorganic modeler to search for different conformational and geometric isomers within a single simulation. In the preponderance of cases, both MM conformational searching techniques (LIGB and high-temperature MD/SA) provide rapid and complete searching. The LIGB approach is superior for macrocyclic complexes.

(2) A genetic algorithm optimized PM3(tm) parametrization for Tc is compared with the standard implementation. The results indicate that for the most prevalent Tc structural motifs (i.e., five- and six-coordinate structures with a single Tc atom) significant improvement in structural predictive ability can be obtained using a GA optimization scheme for SEQM parameters.

(3) The utility of the MM−SEQM coupled approach for rapid (most calculations take on the order of several hours from start to finish per Tc complex), efficient, and effective *de novo* structural prediction is assessed. Furthermore, the coupling of an MM conformational searching technique for fast, initial screening of Tc complexes based on their steric favorability, followed by SEQM geometry optimization of sterically feasible geometries, seems to be superior than either method in isolation. In many cases, the simple MM force field used in this research is unable to predict the correct geometric isomer. Of course, it is quite conceivable that a more rigorous force field could be derived to correctly discriminate geometric isomers. An SEQM-only search, on

(36) *WACXIH*: White, D. J.; Kuppers, H. J.; Edwards, A. J.; Watkin, D. J.; Cooper, S. R. *Inorg. Chem.* **1992**, *31*, 5351.
(37) *ZOPWAC*: Barrera, J.; Burrell, A. K.; Bryan, J. C. *Inorg. Chem.* **1996**, *35*, 335.
(38) *BUMCER*: Baldas, J.; Boas, J.; Bonnyman, J.; Mackay, M. F.; Williams, G. A. *Aust. J. Chem.* **1982**, *35*, 2413.
(39) *FOPBER*: Colmanet, S. F.; Williams, G. A.; Mackay, M. F. *J. Chem. Soc., Dalton Trans.* **1987**, 2305.
(40) *VATTOZ*: de Learie, L. A.; Haltiwanger, R. C.; Pierpont, C. G. *J. Am. Chem. Soc.* **1989**, *111*, 4324.

the other hand, would be computationally burdensome because these calculations take approximately 2 orders of magnitude longer for comparable molecules (on comparable computer platforms) than molecular mechanics.

The preference for one geometric isomer over another can usually be deduced from relatively simple (e.g., crystal or ligand field theory, d-orbital splitting, frontier molecular orbital arguments, etc.) bonding models. It would be desirable to incorporate "electronic" effects directly into the MM force field for the initial searching because this will be faster than even SEQM calculations. Research toward this goal is underway in our labs.

**Acknowledgment.** The research described here was carried out under the auspices of an "NSF Scholar in Residence at NIH" Grant (CHE-9983664) to T.R.C. T.R.C. further acknowledges the Advanced Biomedical Computing Center for a generous grant of supercomputing time, access to their programs and facilities, and a stimulating sabbatical environment for conducting this research. The assistance of the MacroModel developers in the application of the LIGB method is also gratefully acknowledged. The initial implementation of LIGB/VDWB at Columbia University was motivated by the work of Professor Robert Beer and his student, Matt Walker. P.S.S. gratefully acknowledges their collaboration.

**Supporting Information Available:** Table containing the complete list of 197 Tc complexes used to compare PM3(tm) and PM3(tm)-GA parametrizations, along with their literature reference. This material is available free of charge via the Internet at http://pubs.acs.org.

IC0109748