Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Organometallic Chemistry 691 (2006) 2495–2502
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

A new molecular mechanics force field for the design of oxotechnetium(V) and oxorhenium(V) radiopharmaceuticals

Peter Comba [a,*], André Daubinet [a], Bodo Martin [a], Hans-Jürgen Pietzsch [b], Holger Stephan [b]

[a] Universität Heidelberg, Anorganisch-Chemisches Institut, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
[b] Forschungszentrum Rossendorf, Institut für Radiopharmazie, Postfach 510119, 01314 Dresden, Germany

Received 4 October 2005; received in revised form 13 January 2006; accepted 18 January 2006
Available online 6 March 2006

Abstract

Force field parameters for the modeling of oxotechnetium(V) and oxorhenium(V) complexes with amine, amide, imine, carboxylate and thiolate donors have been derived and optimized based on 131 published solid state structures. An automated procedure, based on a simplex algorithm, was used to optimize the 35 sets of metal-dependent structural parameters for each metal ion. These were introduced into the established MOMEC97 force field. The application of the new force field in the prediction of a novel radiopharmaceutical's structure was successful, the predicted structures of the two isomers compared well with the corresponding crystal structures obtained subsequently (RMS around the metal core: 0.153 and 0.035 Å, respectively).

Keywords: Molecular mechanics; Simplex; Technetium; Rhenium; Radiopharmaceutical

1. Introduction

Due to various possibilities to change their biological behavior, complexes of the radionuclides ^{99m}Tc and $^{186/188}$Re are of increasing importance in the development of radio tracers for diagnostic [1] and therapeutic [2] applications. The availability of ^{99m}Tc from the low cost ^{99}Mo/^{99m}Tc generator, combined with its favorable radiophysical properties and the commercial distribution of pre-prepared instant kits for various clinical examinations, have made ^{99m}Tc a preferred radio label in nuclear medicinal imaging. Similarly, the β-emitting isotope ^{188}Re is easily obtained as perrhenate ion (ReO_4^-) in saline solution from a ^{188}W/^{188}Re generator system [3]. The relatively slow decay of activity of the generator is expected to provide ^{188}Re at reasonably low costs for routine preparation of a variety of radiopharmaceuticals for cancer treatment. Therefore, there is much interest in the development of ^{188}Re radiopharmaceuticals, e.g., site-specific complexes with ligands such as diphosphonates [4] or with chelate ligands attached to biomolecules such as peptides [5] or monoclonal antibodies [6].

The design of ^{99m}Tc/^{188}Re-labeled compounds, which retain their ability for highly specific in vivo targeting of cancer cells, is not trivial. The fundamental challenge is the pharmacologically acceptable integration of these transition metal coordination compounds into the molecular entity of bio-macromolecules. In addition, the dependence from the coordination geometry of the various factors, which influence the biological activity of oxotechnetium and oxorhenium complexes, such as molecular shape, overall charge and charge distribution, is of great importance and a topic of current studies [7].

Structural modeling and structure-property correlations (QSPR) have become a powerful tool for the design of new compounds and for the interpretation and fine-tuning of their properties. Due to the simplicity, the accuracy of structural predictions and the general availability, molecular mechanics (MM) and combinations of MM with the

* Corresponding author. Tel.: +49 6221 548453; fax: +49 6221 91014/546617.
E-mail address: peter.comba@aci.uni-heidelberg.de (P. Comba).

0022-328X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2006.01.068

computation of properties, based on accurate structures have gained increasing importance, in particular in the area of coordination chemistry [8–13]. Force fields for rhenium and technetium have been developed for various modeling packages but were mostly tailored for specific compound sets [14–18]. To develop a new, more general force field is a laborious task, and the development of force field parameters with a simple and robust automated procedure is of great use [19–23]. Our aim was to develop a method for deriving force field parameters, based on simple programming building blocks, which could be used on a wide range of available software platforms, and for general force field parameter generation.

We present here a general force field for the oxotechnetium(V) and oxorhenium(V) classes of compounds, obtained via this methodology. The force field was tested with two structures from the Cambridge structural data base, not used in the force field development, and used to predict two novel structures which subsequently were determined experimentally [24,25].

2. Computational procedures

2.1. Software and resources

The software for parameter optimization was chosen to be as platform-independent as possible and, where necessary, easily adaptable. Therefore, the program was implemented using the scripting language Perl [26], which is available for a wide range of operating systems.

Our own molecular mechanics program MOMEC97 (version 2.3.1) [27] and force field [28–30] were chosen for structure optimization. Other modules used include: the Cambridge structural database (CCDC) [31]; CYGWIN version 1.5.9-1 [32]; the Math-Amoeba-0.01 Perl module (implementation of the Simplex strategy [26]) HYPERCHEM 4.5 [33]; GAUSSIAN'98/'03 [34]; standard PC, Linux cluster.

2.2. Crystal structures/learning set

There are 49 and 82 crystal structures of oxotechnetium(V) and oxorhenium(V) complexes, respectively, which have been used for the parameterization of the force field. These were retrieved from the Cambridge Crystallographic Database (the complete list of entries is given as Supplementary data). Further structures were obtained from the crystal structure collection of the Forschungszentrum Rossendorf (FZR) [35]. The crystal structures were converted into the Hyperchem HIN format; counter ions and solvent molecules of crystallization were removed.

2.3. Force field development

Within the MOMEC97 [27] MM program the total strain energy (Eq. (1)) of a molecule is calculated from the sum of the bond deformation (E_b), angle deformation (E_a), torsion angle deformation (E_t) and non-bonded interaction energies (E_{nb}). Terms for out-of-plane deformation, electrostatic interactions and hydrogen bonding were excluded in the present study. Atom type labels for the organic components of the systems were assigned according to the previously published atom types [28–30,36–43], new atom types were assigned as illustrated in the Supplementary material, Fig. S1.

$$E_{\text{Strain}} = \sum E_b + \sum E_a + \sum E_t + \sum E_{nb}, \quad (1)$$

where

$$E_b = \frac{1}{2}k_S(r_c - r_0)^2,$$

$$E_a = \frac{1}{2}k_B(\theta_c - \theta_0)^2,$$

$$E_t = \frac{1}{2}k_T(1 - \cos(m\phi_c - \phi_0)),$$

$$E_{nb} = \frac{q_i q_j}{\varepsilon r} + Ar_{ij}^{-12} + Br_{ij}^{-6},$$

where k_S, k_B, k_T are the potential constants and r_0, θ_0, ϕ_0 are the respective ideal values.

The parameter optimization program consists of three modules:

Table 1
Accuracy and weighting factors

Parameter	Assumed error limit	Weighting factor
Bond length	0.01 Å	100
Valence angle	1°	1
Torsion angle	5°	0.2

Table 2
Periodicity and offset angle value for the torsional functions

Torsion	Atom types	Periodicity	θ_{Offset} (°)
M_{C4v}–N_{C2v}	N^{amide}, N^{imine}, $N^{pyridyl}$	8	22.5
M_{C4v}–N_{C3v}	N^{amine}	12	0
M_{C4v}–S_{C1v}	S^{cys}	4	45
M_{C4v}–S_{C3v}	S^{met}	12	0

M = Tc, Re.

Table 3
Bond stretch parameters

		Force constant k (kJ mol^{-1} Å^{-2})	Reference bond distance r_0 (Å)	Data points	χ^2
Re	O^{oxo}	1716	1.685	93	304
Re	N^{amide}	1445	1.950	63	1050
Re	N^{amine}	602	2.100	46	277
Re	$N^{pyridyl}$	662	2.030	5	46
Re	S^{cys}	1024	2.265	244	470
Re	S^{met}	1188	2.353	14	54
Tc	O^{oxo}	2829	1.663	50	140
Tc	N^{amide}	334	1.821	69	1259
Tc	N^{imine}	1796	2.062	26	25
Tc	N^{amine}	346	2.036	23	205
Tc	S^{cys}	909	2.250	82	551

Table 4
Angle bending parameters

			Force constant k (kJ mol^{-1} deg)	Reference angle θ_0 (°)	Data points	χ^2
N^{amide}	Re	N^{amide}	131	90	25	76
N^{amide}	Re	N^{amine}	75	90	18	159
N^{amide}	Re	$N^{pyridyl}$	79	90	2	22
N^{amide}	Re	S^{met}	71	90	12	143
S^{cys}	Re	N^{amide}	116	90	107	1127
S^{cys}	Re	$N^{pyridyl}$	45	90	13	225
S^{cys}	Re	N^{amine}	87	90	121	2307
S^{cys}	Re	S^{cys}	110	90	231	4289
S^{cys}	Re	S^{met}	81	90	30	152
O^{oxo}	Re	N^{amide}	128	90	63	681
O^{oxo}	Re	$N^{pyridyl}$	2	90	5	148
O^{oxo}	Re	N^{amine}	210	90	46	492
O^{oxo}	Re	S^{cys}	139	90	244	2875
O^{oxo}	Re	S^{met}	69	90	14	419
Re	N^{amide}	C^{sp2}	116	135	15	16
Re	N^{amide}	C^{amide}	452	120	38	265
Re	N^{amide}	C^{sp3}	301	120	74	988
Re	$N^{pyridyl}$	C^{sp2}	164	123	10	14
Re	N^{amine}	C^{sp3}	301	109	129	802
Re	N^{amine}	H	241	109	9	448
Re	S^{cys}	C^{sp2}	241	109	57	261
Re	S^{cys}	$C^{carbonyl}$	166	109	4	53
Re	S^{cys}	C^{sp3}	307	109	184	957
Re	S^{met}	C^{sp3}	331	109	29	297
N^{amide}	Tc	N^{amide}	131	90	48	1663
N^{amide}	Tc	N^{imine}	37	90	52	360
N^{amide}	Tc	N^{amine}	75	90	9	27
N^{amine}	Tc	N^{amine}	18	90	4	10
N^{imine}	Tc	N^{imine}	288	95	13	44
S^{cys}	Tc	N^{amide}	116	90	50	1411
S^{cys}	Tc	N^{amine}	87	90	52	2253
S^{cys}	Tc	S^{cys}	55	85	72	1371
O^{oxo}	Tc	N^{amide}	155	109	69	1034
O^{oxo}	Tc	N^{imine}	130	107	26	86
O^{oxo}	Tc	N^{amine}	105	101	23	777
O^{oxo}	Tc	S^{cys}	246	108	82	1024
Tc	N^{amide}	C^{sp2}	133	117	8	54
Tc	N^{amide}	C^{amide}	198	124	28	5
Tc	N^{amide}	C^{sp3}	301	120	96	1449
Tc	N^{amide}	H	60	122	6	395
Tc	N^{imine}	C^{sp2}	92	118	26	282
Tc	N^{imine}	O	94	123	26	152
Tc	N^{amine}	C^{sp3}	73	110	59	677
Tc	N^{amine}	H	152	105	7	360
Tc	S^{cys}	C^{sp2}	140	103	20	328
Tc	S^{cys}	$C^{carbonyl}$	93	98	4	0
Tc	S^{cys}	C^{sp3}	231	107	58	0

(1) The master control module is responsible for the control and flow of data between the modeler (MM program) and the parameter optimizer, and the determination of the error function (χ^2) between calculated and reference structures (Eq. (2)).
(2) The modeler, i.e., MOMEC97 [27], used to calculate the model data.
(3) The optimizer, used to optimize the force field parameter values

$$\chi^2 = \sum_n \omega^2 (r_i - r_0)^2, \quad (2)$$

where ω is the weighting factor (see Table 1), r_i the calculated value and r_0 is the reference value.

Initial values for the force constants and structural parameters were estimated by inspection of the learning structural data set. For the reference bond stretch and angle bending values (equilibrium distances and angles),

the median value, calculated from the crystal structures for a given parameter, were used (see Supplementary material, Tables S2 and S3). The periodicity and offset values for the torsional angles were assigned as given in Table 2; these were derived from simple generic considerations and fundamental principles of bonding theory [8]. To ensure that consistent force field parameter values had been obtained, various sets of parameter starting values were chosen and the optimization repeated until the lowest error function value was obtained. The ability of the force field to reliably predict structures was tested with selected structures not used as part of the learning set. These were computed and compared to the experimental data (see Supplementary material, Tables S4 and S5).

3. Results and discussion

3.1. Force field development

The aim, when developing MM force field parameters for structural modeling, is the determination of an optimum combination of parameters, which successfully reproduce known (experimental) structures to a high degree of accuracy. For systems described by only a few missing parameters, based on an existing general force field, this is invariably a simple task and can be done by manual fitting procedures [23]. When the number of variables and unknown parameters increases, as in the case of this study, the task becomes non-trivial. Here, the use of a mathematical tool in form of an optimizer can be of great assistance. One such mathematical approach is the simplex method [26,44], which only requires a function that describes the relationship between the variables to be optimized. In theory, the method allows for an unlimited amount of variables to be solved, but in practise the limit lies with about 30 variables. The parameterization was therefore conducted in an incremental fashion, using initially small subsets of related parameters, i.e., for systems containing similar ligand donor atom combinations. Once these parameters had been optimized, further combinations of parameters were included in the optimization. This successive parameter optimization was repeated until an optimum combination of parameters was achieved. In Tables 3–5 are listed the optimized force field parameters derived from 82 rhenium(V) and 49 technetium(V) structures (see Supplementary material), with the corresponding error function parameter χ^2 for each parameter. Generally, torsional potentials around metal-donor bonds are set to zero, i.e., there is no penalty for the rotation around metal-donor bonds. While this is reasonable for pure δ-donors, π-bonding contributions need in principle to be included in the force field [8]. This has been found to be essential in the case of accurate modeling of Tc(V) complexes [17,18].

An ideal parameterization is achieved when χ^2 equals the number of data points for each parameter. Only for few of the tabulated parameters the result is close to this limit. Potential reasons for significant deviations include: (a) a local rather than the global minimum was found by the optimizer, (b) poor experimental structural data (this may include examples where the experimental data correspond to a local minimum, enforced by the crystal lattice).

Table 5
Torsion angle parameters

		Force constant k (kJ mol^{-1})	Periodicity m	Offset θ_0 (°)	Data points	χ^2
Re	N^{amide}	0.0301	8	22.5	504	1803
Re	N^{amine}	0.0301	12	0.0	552	3513
Re	$N^{pyridyl}$	0.0301	8	22.5	40	68
Re	S^{cys}	9.6352	4	45.0	976	3275
Re	S^{met}	1.2044	12	0.0	112	2325
Tc	N^{amide}	0.3011	8	22.5	552	5223
Tc	N^{amine}	0.3011	12	0.0	264	11556
Tc	N^{imine}	0.0602	8	22.5	208	2812
Tc	S^{cys}	3.0110	4	45.0	328	4823

In order to demonstrate the quality of the force field, two structures, not used in the parameterization, were computed and the corresponding error functions χ^2 determined. For rhenium(V) the CSD entry RERSEM and for technetium(V) the CSD entry JAWMID were used (results are given in Table 6). Illustrations of the structures are shown in Figs. 1 and 2 and complete structural data are given as Supplementary information (Tables S4 and S5). The RERSEM structure is reproduced with lower error values χ^2 than for the general force field parameterization, while the JAWMID structure is reproduced with larger values of χ^2, which on inspection was shown to be due in part to the distortion of the very flexible organic backbone, leading to a very complex conformational space (see Fig. 1d). Inspection of the geometry of the chromophore indicates that it is reproduced rather accurately.

Table 6
Calculated error functions for the rhenium(V) test compound RERSEM and the technetium(V) test compound JAWMID

Parameter					Data points	χ^2
Stretch	O^{oxo}	Re			1	0.6
	S^{cys}	Re			3	6.3
	N^{amine}	Re			1	7.2
Bend	O^{oxo}	Re	S^{cys}		3	3.0
	O^{oxo}	Re	N^{amine}		1	2.7
	S^{cys}	Re	S^{cys}		3	10.8
	S^{cys}	Re	N^{amine}		3	3.1
Torsion	**	Re	S^{cys}	**	9	22.4
	**	Re	N^{amine}	**	4	3.8
Stretch	O^{oxo}	Tc			2	12
	S^{cys}	Tc			8	118
Bend	O^{oxo}	Tc	S^{cys}		8	20
	S^{cys}	Tc	S^{cys}		12	66
Torsion	**	Tc	S^{cys}	**	32	2989

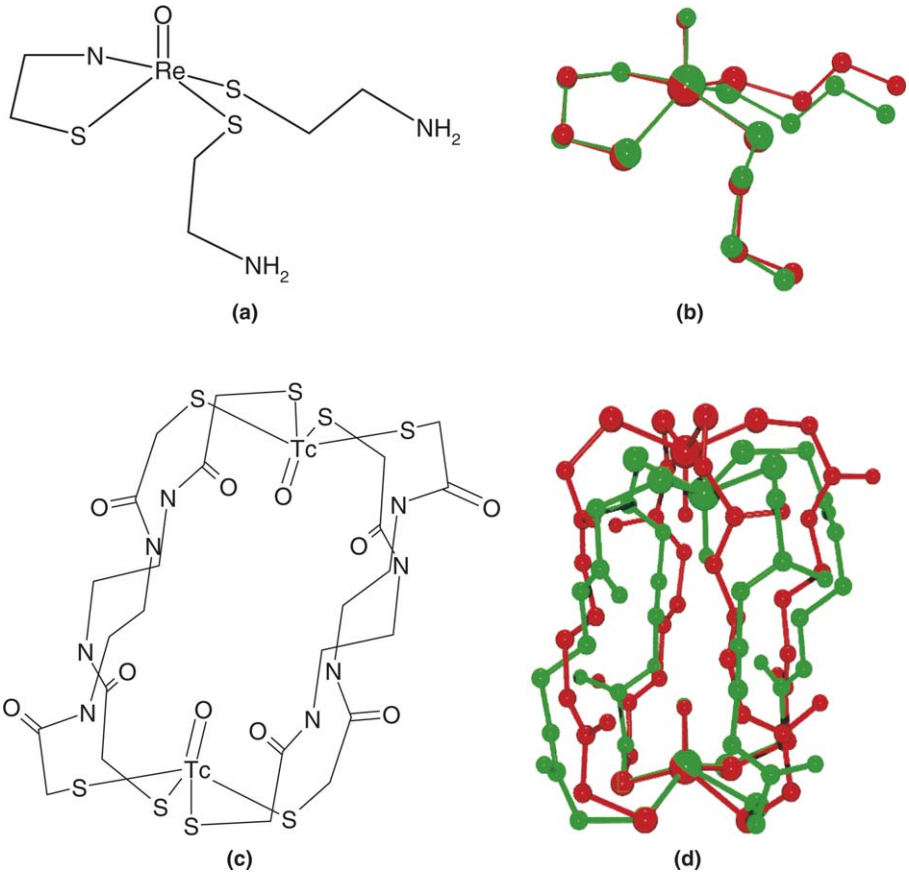

Fig. 1. Structures of the oxorhenium(V) and oxotechnetium(V) complexes used for the validation of the force field: (a, b) CSD entry RERSEM, (c, d) CSD entry JAWMID. In the overlay plots (b, d), the experimental structures are green, the computed structures are red, hydrogen atoms have been removed for clarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Derivatives of meso 2,3-dimercaptosuccinic acid

Dimercaptosuccinate (DMSA) is a well-known ligand which forms stable complexes with Tc^{V}=O [45] and Re^{V}=O [45]. The tumor-selective agents $[M{=}O(DMSA)_2]^-$ have found clinical application for imaging (M = ^{99m}Tc) [46] and therapy (M = ^{186}Re, ^{188}Re) [47–49]. A new approach to exploit $[^{99m}Tc{=}O(DMSA)_2]^-$ as a potential radiopharmaceutical drug consists in the functionalization of the DMSA ligand with ester groups. Recent studies have shown that the introduction of one or two non-hydrolysable ester groups into the $[^{99m}Tc^{V}{=}O(DMSA)]^-$ molecule leads to a decrease of bone accumulation without deterioration of the tumour uptake [50].

Based on the high in vivo stability of $[^{188}Re{=}O(DMSA)_2]^-$ we started to investigate this system for the design of novel chelate ligands and $^{188}Re^{V}$=O complexes which are stable with respect to re-oxidation to perrhenate and ligand exchange under all conditions of radiopharmaceutical procedures and applications. MM can be used for the rational design of tailor-made ligand structures, which enable: (i) the highly stable, pharmacologically acceptable linking of ^{99m}Tc or ^{188}Re to bio-molecules and (ii) the fine-tuning of physico-chemical parameters of the radiotracers, such as solubilities, dissociative partition coefficients, lipophilicities and protein binding.

As a first step a novel type of tetrathiolate ligand was prepared by bridging two dimercaptosuccinates with an alkylenetriamine chain, as illustrated in Fig. 2 [24]. Of particular interest was the ligand *N*-[3-{3-(3-diisobutylcarbamoyl-2,3-dimercapto-propionylamino)propylamino}-propyl]-*N*′,*N*′-diisobutyl-2,3-dimercaptosuccinamide (*R*,*S*-L^1), shown in Fig. 2b [24]. Using the force field described above, the structure and isomer distribution of the $[Re^{V}{=}O(R,S\text{-}L^1)]^-$ complex were computed; possible isomers are shown in Fig. 2c. The computed isomer distribution is reported in Table 7, Fig. 3 presents the structures of the two complexes which are compared to the experimental data in Table 8. Inspection of Table 7 reveals that there is a clear trend for $[Re^{V}{=}O(R,S\text{-}L^1)]^-$ to adopt the *exo*-conformation, irrespective of whether the ligand binds in *cis* or *trans* configuration to the metal. In both the *cis* and *trans* systems there is a significant steric energy difference between the *endo* and *exo* forms, of the order of >10 kJ/mol.

These predictions were confirmed by two crystal structures of $[Re^{V}{=}O(R,S\text{-}L^1)]^-$ [24]. Illustrated in Fig. 3 are

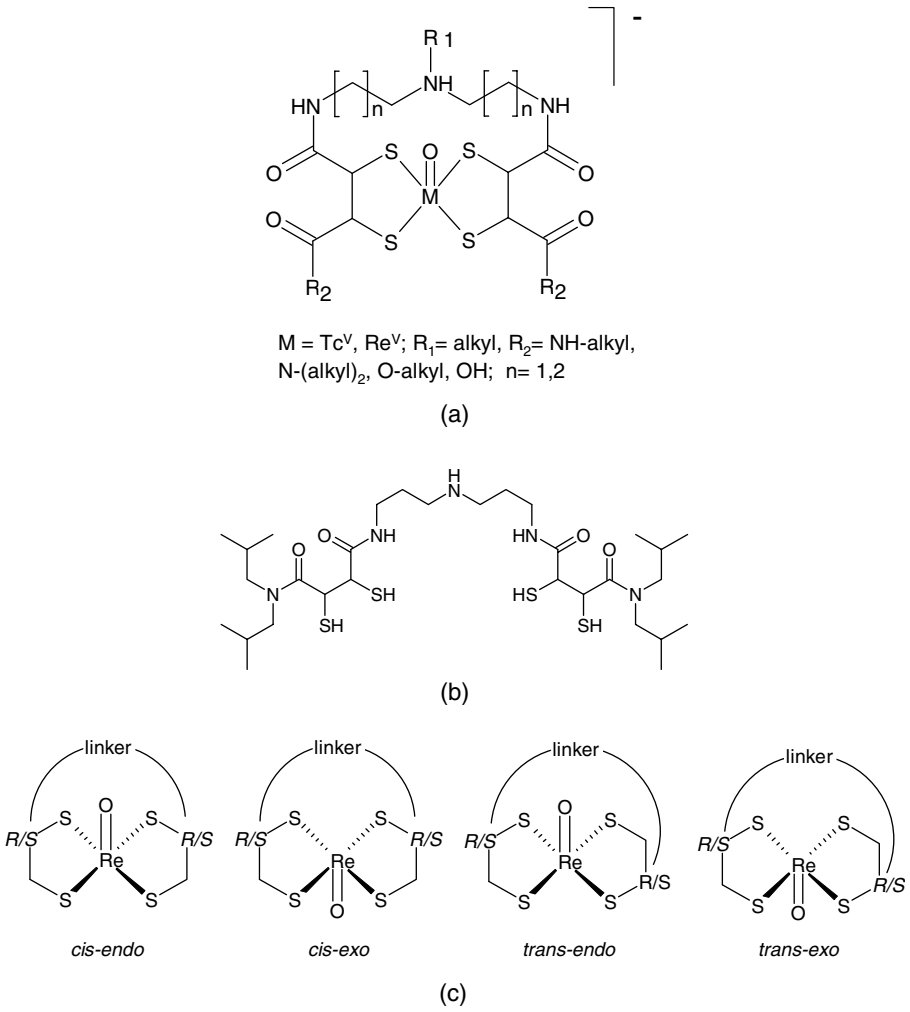

Fig. 2. (a) A new class of DMSA-based Tc^V and Re^V complexes; (b) the *R*,*S*-L^1 ligand used in this study [21]; (c) the isomers *cis*, *trans*, *exo* and *endo* isomers considered for the model calculations of $[Re^V{=}O(R,S\text{-}L^1)]^-$; the chirality at the attachment points of the linker chain was also considered.

Table 7
Calculated steric energies of the isomers of $[Re^V{=}O(R,S\text{-}L^1)]$

Linker chirality	*cis*		*trans*	
	endo (kJ mol^{-1})	*exo* (kJ mol^{-1})	*endo* (kJ mol^{-1})	*exo* (kJ mol^{-1})
RS–**RS**	60	27	15	1
RS–**SR**	10	4	–	–
SR–**RS**	6	0	–	–
SR–**SR**	58	27	16	4

*The highlighted label indicates the attachment point of the linker.

the crystal structures of the *cis* and *trans* complexes together with the corresponding structural predictions. In Table 8 are listed the calculated errors between the modeled structures and the crystal structures. The larger than usual error in the oxygen–rhenium bond distance of the *trans* isomer (1.565 Å) is attributed to an unusually short bond in the crystal structure, as compared to the median for the learning set. All other parameters fall within the error range of the force field.

4. Conclusions

A new module is presented which allows to optimize a force field based on structural parameters, for MM force fields in general and specifically for the MOMEC force field. This has been used to develop new parameters for oxotechneticum(V) and oxorhenium(V) radiopharmaceuticals, based on the existing MOMEC parameterization scheme [8,27,30]. The force field has been validated with structures not used for the parameterization process and it has also been shown to produce results which are of similar quality as a known parameterization scheme for Tc(V) radiopharmaceuticals, which is known to lead to accurate predictions [17,18]. Most importantly, it has been used for the highly accurate prediction of the structures of two new potential radiopharmaceuticals, whose conformations and structural parameters were accurately predicted [25]. The correct prediction of the observed isomer is a particular interest, and this probably is related to the balance between the established parameterization of the organic ligand backbone and that of the metal-ligand force field. This in turn has its

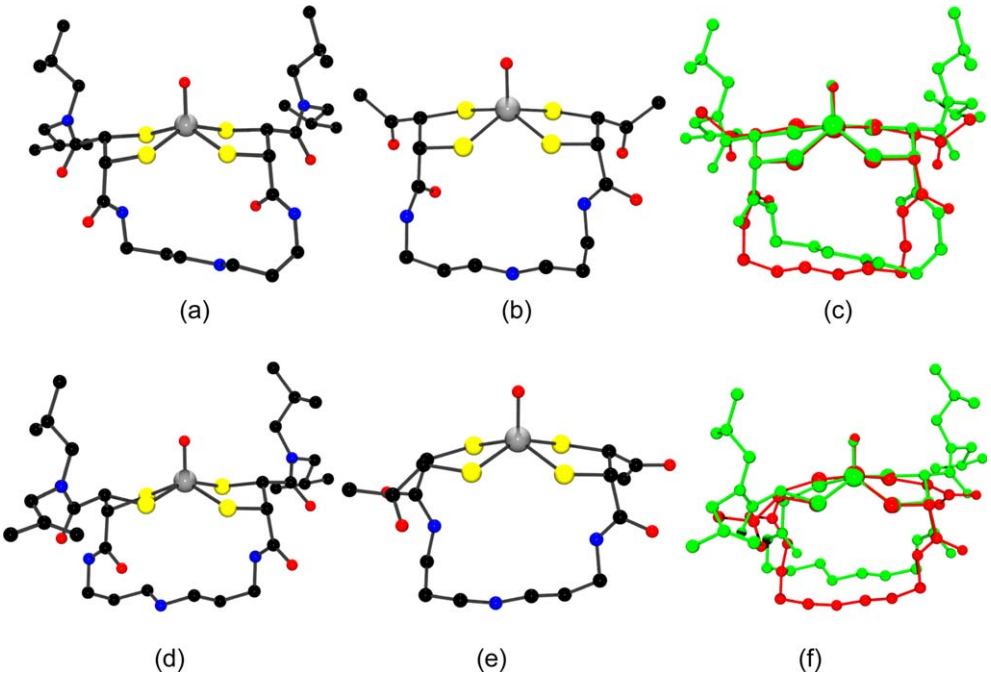

Fig. 3. Structures of the *cis–exo* (a–c) and *trans–exo* (d–f) isomers of $[Re^{V}{=}O(R,S\text{-}L^{1})]^{-}$: (a, d) crystal structures; (b, e) computed structures (pendant arms not included), (c, f) overlay plot of crystal (green) and computed (red) structures (hydrogen atoms have been removed for clarity). RMS (around metal centre): 0.153 and 0.035 for *cis–exo* and *trans–exo*, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 8
Calculated error function for the *cis* and *trans* isomers of $[Re^{V}{=}O(R,S\text{-}L^{1})]$

Parameter					Data points	χ^2	
						cis	*trans*
Stretch	O^{oxo}	Re			1	0.4	156.3
	S^{cys}	Re			4	17.4	16.4
Bend	O^{oxo}	Re	S^{cys}		4	22.7	28.8
	S^{cys}	Re	S^{cys}		12	96.4	127.7
Torsion	**	Re	S^{cys}	**	16	10.5	14.6

RMS around metal core: *cis* = 0.153; *trans* = 0.035.

origin in well tuned parameters, also involving thermodynamic observables, and the metal-centered parameters [8,11,23]. We emphasize, however, that this may be fortuitous, since crystal packing forces can lead to the stabilization of a particular conformation in the solid. These results will allow for further tuning of the ligand system for improved properties in the area of nuclear medicine. An important factor with respect to the biological activity is the charge distribution in radiopharmaceuticals [7]. We are currently developing semi-empirical methods for the accurate and quick calculation of charge distributions which will be introduced in our molecular mechanics program.

Acknowledgement

Financial support by the Deutsche Forschungsgemeinschaft (DFG) is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2006.01.068.

References

[1] S.S. Jurisson, J.D. Lydon, Chem. Rev. 99 (1999) 2205.
[2] W.A. Volkert, T.J. Hoffman, Chem. Rev. 99 (1999) 2269.
[3] F.F. Knapp, A.L. Beets, S. Guhlke, P.O. Zamora, H. Bender, H. Palmedo, H.J. Biersack, Anticancer Res. 17 (3B) (1997) 1783.
[4] E.C. Lisic, M. Phillips, D. Ensor, K.L. Nash, A. Beets, F.F. Knapp, Nucl. Med. Biol. 28 (2001) 419.
[5] H. Bender, P.O. Zamora, B.A. Rhodes, S. Guhlke, H.J. Biersack, Anticancer Res. 17 (3B) (1997) 1705.
[6] U. Seitz, B. Neumaier, G. Glatting, J. Kotzerke, D. Bunjes, S.N. Reske, Eur. J. Nucl. Med. 26 (1999) 1265.
[7] M. Lipowska, L. Hansen, X. Xu, P.A. Marzilli, A.T. Taylor, L.G. Marzilli, Inorg. Chem. 41 (2002) 3032.
[8] P. Comba, T.W. Hambley, Molecular Modeling of Inorganic Compounds, second ed., with a Tutorial, based on MOMEClite', Wiley-VCH, 2001.
[9] A.K. Rappé, C.J. Casewit, Molecular Mechanics Across Chemistry, University Science Books, 1997.
[10] C.R. Landis, D.M. Root, T. Cleveland, in: K.B. Lipkowitz, D.B. Boyd (Eds.), Rev. Comp. Chem., vol. 73, New York, Weinheim, 1995.
[11] J.C.A. Boeyens, P. Comba, Coord. Chem. Rev. 212 (2001) 3.
[12] B.P. Hay, O. Clement, in: E. Schleyer (Ed.), The Encyclopedia of Computational Chemistry, Wiley, 1998.
[13] R. Deeth, J.A. McCleverty, T.J. MeyerComprehensive Coordination Chemistry II, vol. 2, Elsevier, 2003, p. 457.
[14] M. Lipowska, L. Hansen, R. Cini, X. Xu, H. Choi, A.T. Taylor, L.G. Marzilli, Inorg. Chim. Acta 339 (2002) 327.

[15] L.G. Marzilli, G.B. Mariusz, L. Hansen, Z. Kuklenyik, R. Cini, A.J. Tayler, Inorg. Chem. 33 (1994) 4850.
[16] L. Hansen, R. Cini, A.J. Taylor, L.G. Marzilli, Inorg. Chem. 31 (1992) 2801.
[17] D.E. Reichert, M.J. Welch, Coord. Chem. Rev. 212 (2001) 111.
[18] R.D. Hancock, D.E. Reichart, M.J. Welch, Inorg. Chem. 35 (1996) 2165.
[19] S. Lifson, A. Warshel, J. Chem. Phys. 49 (1968) 5116.
[20] P.-O. Norrby, T. Liljefors, J. Comp. Chem. 19 (1998) 1146.
[21] P.-O. Norrby, P. Brandt, Coord. Chem. Rev. 212 (2001) 79.
[22] P.-O. Norrby, in: E.T.R. Cundari (Ed.), Recipe for an Organometallic Force Field, New York, Basel, 2001.
[23] P. Comba, R. Remenyi, Coord. Chem. Rev. 238–239 (2003) 9.
[24] T. Heinrich, W. Kraus, H.-J. Pietzsch, C. Smuda, H. Spies, Inorg. Chem. 44 (2005) 9930.
[25] The fact that the experimental studies [24] and the computational work presented here were done independently at Rossendorf and Heidelberg, respectively, and that the corresponding structural data were only exchanged after completion of the respective studies and not modified subsequently, is a statement which cannot be proven.
[26] J.A. Nelder, R. Mead, Comput. J. 7 (1965) 308.
[27] P. Comba, T.W. Hambley, G. Lauer, N. Okon, MOMEC97, A Molecular Modeling Package for Inorganic Compounds, University Heidelberg, 1997.
[28] P.V. Bernhardt, P. Comba, Inorg. Chem. 31 (1992) 2638.
[29] P. Comba, T.W. Hambley, M. Ströhle, Helv. Chim. Acta. 78 (1995) 2042.
[30] J.E. Bol, C. Buning, P. Comba, J. Reedijk, M. Ströhle, J. Comput. Chem. 19 (1998) 512.
[31] The Cambridge Crystallographic Data Centre, Cambridge CB2 1EZ, UK.
[32] CYGWIN Version 1.5.9-1. Available from: <www.cygwin.com>.
[33] HYPERCHEM 4.5, Hypercube. Inc., Gainsville FL, USA, 2003.
[34] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, GAUSSIAN 98, Revision A.6, Pittsburgh, PA, 1998.
[35] P. Leibnitz, G. Reck, H.-J. Pietzsch, H. Spies, Report FZR-311, 2001.
[36] P. Comba, H. Jakob, B. Nuber, B.K. Keppler, Inorg. Chem. 33 (1994) 3396.
[37] P. Comba, Inorg. Chem. 33 (1994) 4577.
[38] P. Comba, M. Zimmer, Inorg. Chem. 33 (1994) 5368.
[39] P. Comba, T.W. Hambley, P. Hilfenhaus, D.T. Richens, J. Chem. Soc., Dalton Trans. (1996) 533.
[40] P. Comba, P. Hilfenhaus, K.D. Karlin, Inorg. Chem. 36 (1997) 2309.
[41] P. Comba, K. Gloe, T. Inoue, H. Stephan, K. Yoshizuka, Inorg. Chem. 37 (1998) 3310.
[42] P. Comba, T. Gyr, Eur. J. Inorg. Chem. (1999) 1787.
[43] P. Comba, R. Remenyi, J. Comput. Chem. 23 (2002) 697.
[44] G.B. Dantzig, Linear Programming and Extensions, Princeton University Press, 1963.
[45] H. Spies, D. Scheller, Inorg. Chim. Acta 116 (1986) 1.
[46] J. Singh, A.K. Powell, S. Clarke, P.J. Blower, J. Chem. Soc. – Chem. Commun. 16 (1991) 1115.
[47] O.A. Mojiminiyi, R. Udelsman, N.D. Soper, B.J. Shepstone, N.E. Dudley, Clin. Nucl. Med. 16 (4) (1991) 259.
[48] P.J. Blower, A.S.K. Lam, M.J. O'Doherty, A.G. Kettle, A.J. Coakley, F.F. Knapp, Eur. J. Nucl. Med. 25 (1998) 613.
[49] P.J. Blower, A.G. Kettle, M.J. O'Doherty, A.J. Coakley, F.F. Knapp, Eur. J. Nucl. Med. 27 (2000) 1405.
[50] S. Seifert, R. Syhre, H. Spies, B. Johannsen, Nucl. Med. Commun. 24 (11) (2003) 1175.