A Molecular-Mechanics Approach for the Prediction of the Geometry of High-Spin Fe^{III} Complexes with Oxygen and Nitrogen as Coordinating Atoms

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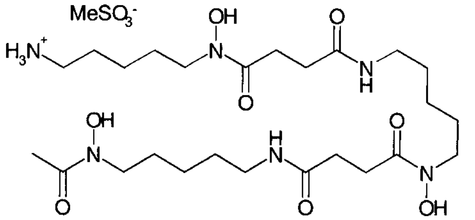
A method for the prediction of geometries and the *de novo* design of oligodentate ligands for octahedral high-spin Fe^{III} complexes with chemically diverse coordinating functions is described. Based on a set of 23 complexes with two nitrogens and four oxygens as coordinating atoms, a computational method was elaborated that describes and predicts the geometries of high-spin Fe^{III} complexes, including small variations in bond length and angles. The method uses partial atomic charges of the ligand, which are obtained from *ab initio* calculations, and empirically derived angular and dihedral constraints, which are added to a molecular-mechanics force field. Conformational analyses of the complex geometries were performed. The method was iteratively optimized by fitting calculated geometries into the corresponding crystal structures of the Fe^{III} complexes. Three representative examples of calculated structures superimposed on the crystal structure are shown to illustrate the accuracy of the method.

Introduction. – Whereas iron uptake in the GI-tract appears to be highly regulated, there is no active mechanism in man for iron excretion [1]. Repeated blood transfusions or excessive dietary iron uptake in anemias and hereditary hemochromatosis can lead to toxic and eventually lethal amounts of iron. Patients who are affected by the hereditary thalassemia major [2] have unstable hemoglobin and need repeated blood transfusions. If untreated, the resulting iron overload leads to serious complications and early death. *Desferal*® (**1**)[1]) is the only iron-chelating drug approved for general use. However, its very short plasma half-life and its poor oral bioavailability make special modes of application necessary. It usually has to be injected subcutaneously or intravenously during more than 8 h every day, resulting in poor compliance with the drug. *Deferiprone* or *L1* (**2**)[2]) is a competitor of *Desferal*® (**1**), mainly because it is orally



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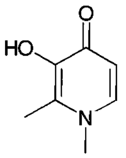

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[1]) Desferrin, deferoxamine, deferoxamide B, desferrioxamin; *CA* Name: *N'*-[5-[[4-[[5-(acetylhydroxyamino)-pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-*N*-(5-aminopentyl)-*N*-hydroxybutanediamide

[2]) 1,4-Dihydro-3-hydroxy-1,2-dimethylpyridin-4-one.

bioavailable, even though it has a low efficiency and is relatively toxic [3]. An efficient, orally active iron chelator would meet a clear medical need, as it would be much better accepted by the patients and could be used also in areas with less developed infrastructure.

A research program with the goal to identify an orally active iron chelator has been under way at the *Novartis* research site in Basel. Parallel to extensive screening of natural products and chemical modification of orally inactive or highly toxic iron chelators, computational chemistry was involved with the aim of designing new iron chelators and rationalizing differences in iron-binding affinities.

Background. – A computational method was, therefore, needed that allows for the calculation of various octahedral Fe^{III} complexes with diverse ligands, with variable coordinative atoms, functions, and denticities. Many studies describing the application of molecular-mechanics force-field calculations in coordination chemistry in general [4], as well as for iron complexes, have been published. However, most of these published methods have been optimized for a very specific set of ligands, *e.g.*, for the calculation of low-spin Fe^{II} and Fe^{III} heme complexes [5]. For this purpose, molecular-mechanics parameters for a specific and very small set of functional groups have been generated. Only one reference for the molecular-mechanics calculation of high-spin ferric complexes was found in the literature [6]. The method is based on radial and angular constraints that were derived by comparison and refinement of modeled complexes with crystal structures. The charges seem to be treated differently for every complex³). None of the published methods based on molecular-mechanics force-field calculations appeared to be generally applicable, leading to geometries of diverse Fe^{III} complexes that were accurate enough to attempt *de novo* design of yet unknown Fe^{III} chelators.

Our attempts to model complex structures with semi-empirical methods that comprise parameters for transition-metal ions [7] were not encouraging. The application of density-functional theory was computationally too expensive to calculate the properties of large complexes [8]. Therefore, we had to set up a new, generally applicable method for the *de novo* design of iron chelators that would allow for calculation and geometry prediction of complexes with very different ligands and coordinating functionalities in reasonable time frames.

A set of 23 crystal structures of high-spin complexes of Fe^{III} with two N- and four O-atoms as coordinating atoms was selected from the *Cambridge Structural Database* and extensively analyzed⁴). A summary of selected data of the coordinative bond length and coordinative bond angles is shown in *Table 1* and *Table 2*, respectively. *Table 3* summarizes a selection of observed dihedral angles in these complexes.

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3) Extract from [7]: '*The point charges assigned to the atoms in the ligand were taken from the AMBER force field. The charges on the coordinated atoms and transition metal were then chosen to best fit the experimental values.*'

4) BOXTUD, BOXVEP, CACTIJ, CAHJEA, CIGREP, CUPSUB, EDACFE, EDTAFE01, EDTAFE10, EGFEMG10, EHGLFE10, FEBPIL10, FUCNUM, JOCTEA, KABDIA, KAJCIH, KAJCIH10, VUBREP, VUPJOF, VUPJUL, WEHYAJ, YALGEX, YAZCUX.

Table 1. *Mean Coordinative Bond Length and Deviations Observed in Crystal Structures*

Type of bond	Mean bond length [Å]	Standard deviation	Maximal deviation from mean	Sample number
Fe−OC=O	2.017	0.058	0.096	34
Fe−O−Ar	1.934	0.043	0.117	27
Fe−N(sp^3)	2.209	0.045	0.086	28
Fe−N(sp^2)	2.124	0.031	0.060	13

Table 2. *Mean Coordinative Bond Angles and Deviations Observed in Crystal Structures*

Type of angle	Mean angle [°]	Standard deviation	Maximal deviation from mean	Sample number
O−Fe−O	92.8	7.2	19.9	40
O−Fe−N	88.5	8.6	19.1	38
N−Fe−N	79.2	2.5	4.0	24
C−O−Fe	123.3	7.1	12.8	46
C−N(sp^3)−Fe	107.5	3.4	6.1	36
C−N(sp^2)−Fe	126.4	1.6	2.1	13

Table 3. *Mean Coordinative Dihedral Angles and Deviations Observed in Crystal Structures*

Dihedral angle [°]	Mean angle [°]	Standard deviation	Maximal deviation from mean	Sample number
C−C−O−Fe	2.5	16.1	44.8	33
C−C−N(sp^2)−Fe	−8.1	6.4	10.5	5

The hexadentate ligand H_4tben[5]) (**3**) forms the strong complex [Fe(tben)] [9] with Fe^{III} that may illustrate the variability of the coordinative bond properties (*Fig. 1*). The experimental Fe−O bond length vary between 1.917 and 2.051 Å, even for this ligand with four chemically identical phenol moieties as coordinating groups. The dihedral angles vary in a range of almost 40°. Due to the observed variability, it appeared to be impossible to define pure molecular-mechanics force-field parameters for our purposes.

Initial attempts to model Fe^{III} complexes by constricting the Fe−ligand bond length failed, because they did not sufficiently allow for variations of bond length and angles. These variations, which are observed even for identical functional groups, are related to the charge distribution, to the conformational space of the ligand and the complex, as well as to crystal-packing forces and solvation effects.

A simple model based on molecular-mechanics methods can account for only the conformational strain energies of the ligand and the strain energies that are induced upon complex formation. The effect of the charge distribution on the coordination bond length cannot be represented by pure molecular-mechanics methods, because the atomic charges of force fields depend only on the defined atom types. More accurate charges are needed for a model in which the variability of the coordination bond length depends on the partial atomic charges on the ligand atoms.

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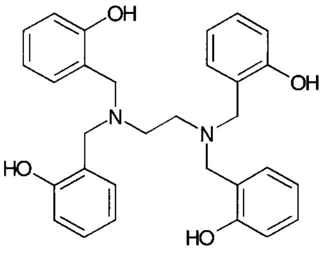
[5]) *N,N,N′,N′*-Tetrakis(2-hydroxybenzyl)ethylenediamine (**3**).



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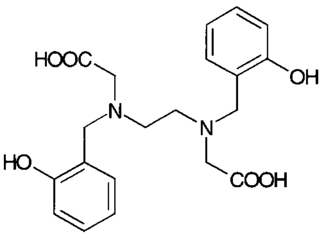

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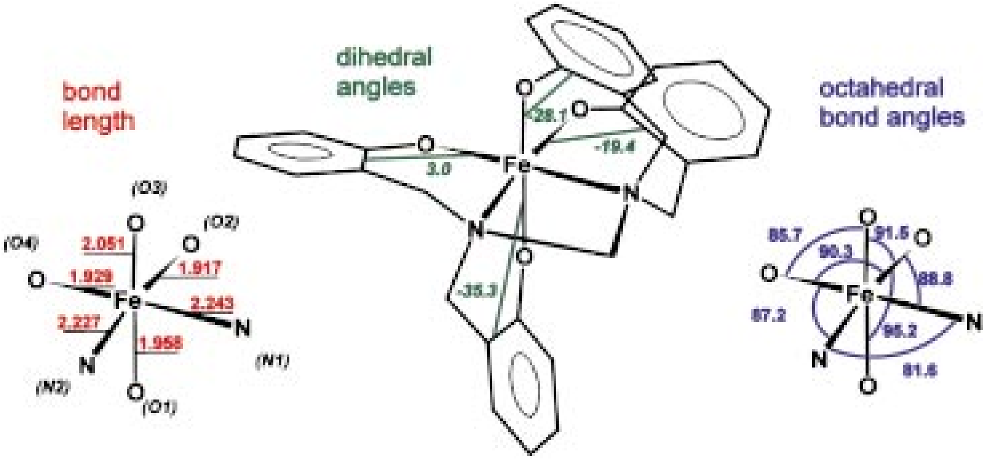

Fig. 1. *Properties of the coordination bond lengths and angles in the crystal structure of [Fe(tben)]*

Method. – When a stable Fe^{III} complex is formed under neutral aqueous conditions, the coordinating OH and COOH groups are usually deprotonated. Calculation of the partial atomic charges of the uncharged ligand would require a modification of the charges when the protons are stripped off. To obviate such an estimation, we decided to calculate the partial atomic charges always for the deprotonated ligand. To generate a simple and generally applicable model, it appeared reasonable to attribute a charge of $+3$ to the central ion, even though the effective atomic charge of Fe^{III} in a complex is expected to be much lower [10]. The combination of the charged ligands with the central ion leads to a complex with the anticipated total charge of the aqua complex.

Partial atomic charges of ionic species cannot easily be estimated with standard semi-empirical methods [11]. *Ab initio* methods offer a better, though computationally more expensive, way to calculate partial atomic charges of charged molecules [12]. The population analysis according to *Merz-Kollman-Singh* [13] was chosen as our standard method for the calculation of the atomic charges.

A molecular-mechanics method based on coulombic interactions may well predict geometries of Fe^{III} complexes with rigid ligands. However, another assumption was made for modeling flexible ligands. The partial atomic charges of flexible ligands are calculated in a low-energy conformation, in which the distances between the charged coordination atoms are maximal and most symmetrical to minimize the electrostatic interaction of the coordinating atoms with each other.

In accordance with the mostly octahedral geometry of the analyzed crystal structures of Fe^{III} complexes, a model has to comprise angular and dihedral constraints to favor this geometry. Flat bottom constraints have been introduced that allow for certain variations around the reference values without any cost in energy. When the deviations become too large, the penalizing energy increases quite rapidly. This procedure leads to complexes with reasonably variable radii and angles that depend mostly on the charges and the strain energies of the ligands.

The goal of this study was to set up a method for *de novo* design, to predict the geometries of unknown complexes, and to evaluate the potential of new ligands for Fe^{III} binding affinities. It was necessary that a heuristically derived set of equal constraints could be applied for all similar angles to allow for geometry prediction of yet unknown complexes. Based on the comparison of crystal structures with modeled complexes, the X–Fe–X bond angles were attributed with a reference value of either $90 \pm 5°$ for neighboring or $180 \pm 5°$ for atoms in opposite positions of the coordination sphere. The constraining force constant was set to 200 kJ/(mol rad) for these angles. All C–O–Fe and C–N(sp^2)–Fe bond angles were constrained to $120 \pm 10°$, and all C–N(sp^2)–Fe bond angles to $105 \pm 10°$ with a force constant of 100 kJ/(mol rad). The dihedral angles C–C–X–Fe were constrained with a force constant of 150 kJ/(mol rad) and a value of $0 \pm 15°$.

The procedure is outlined for the calculation of the Fe^{III} complex with *N,N,N′,N′-tetrakis(2-hydroxybenzyl)ethylenediamine* (H_4tben; **3**).

The central dihedral angle of the N–CH_2–CH_2–N bond was constrained to 180°, and the other dihedral angles were set so that the phenolic O-atoms pointed away from the lone pair of the closest N-atom. This conformation was used as starting point for a N–CH_2–CH_2–N constrained Monte Carlo conformational search. 2000 Monte Carlo steps were performed. After minimization with the *truncated Newton conjugate gradient* (TNCG) [14] and a maximum of 50 minimization steps per conformer with the AMBER* force field [15], the resulting minimal energy conformation was used for the *Merz-Kollman-Singh* population analysis [13] at 6-31G** theory level without further geometry optimization. The resulting conformation, together with the *ab initio* partial atomic charges of the coordinating atoms, is shown in *Fig. 2*. A dummy atom with the charge +3 was added to the ligand and labeled with Fe. The above-mentioned constraints for the dihedral and the bond angles were introduced, and a conformational Monte Carlo search was performed with distance-dependent electrostatics⁶) in the AMBER* force field [15]. 1000 Monte Carlo steps were performed. The *Polak-Ribière conjugate gradient* (PRCG) [16] was used for minimization.

Results and Discussion. – Out of all the generated complex conformations, the resulting energy minimum corresponded most closely to the published crystal structure [9]. The superimposition of these two structures is shown in *Fig. 3*. The radii, as well as the bond and dihedral angles of the computed complex, are compared with the corresponding values of the crystal structure and with the applied constraints in *Tables 4–6*, respectively. The deviations between the experimental and the calculated values fulfilled our requirements for the application of the method in the *de novo* design of iron complexes.

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6) Best results were obtained with $\varepsilon = 1$.

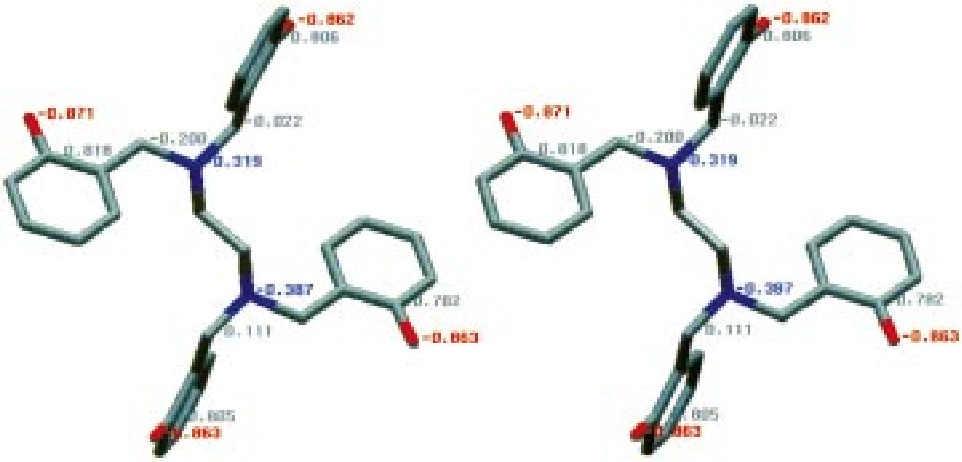

Fig. 2. *The partial atomic charges shown for the coordinating atoms of tben*$^{4-}$ (obtained from electrostatics potential calculation with Gaussian's *Merz-Kollman-Singh* theory). The dihedral angles of the central bonds of the minimized conformation with the $N-CH_2-CH_2-N$ bond constrained to 180° are shown in italics.

Table 4. *Comparison of the Octahedral Bond Lengths between the Computed and the Crystal Structure of [Fe(tben)]*

Distance	Constraint [Å]	Model [Å]	Crystal [Å]	Difference [Å]
Fe–O(1)	none	1.964	1.958	0.006
Fe–O(2)	none	1.961	1.917	0.044
Fe–N(1)	none	2.274	2.243	0.031
Fe–O(3)	none	1.965	2.051	0.086
Fe–N(2)	none	2.278	2.227	0.051
Fe–O(4)	none	1.960	1.929	0.031

A second example is shown in *Fig. 4*, where the high-spin complex of Fe^{III} with H_4hbed (**4**)[7]) [17] is superimposed on its crystal structure [18]. The model was calculated according to the outlined method. Similarly to the first example, it displayed only small deviations from the experimental structure.

A third example, calculated according to the same method, is outlined to demonstrate that the method can also be applied for complex models with more than one ligand molecule per iron ion. The geometry of the rigid, deprotonated L1 (**2**) was optimized and the charges were estimated with the population analysis method by *Merz-Kollman-Singh* [13] with *ab initio* calculation at the 6-31G** level. The optimized ligand was triplicated, and a dummy atom with an atomic charge of +3 was added. The conformations of the complex of Fe^{III} with 3 molecules of L1 were calculated similarly with equal constraints as discussed for H_4tben (**3**). The superimposition in *Fig. 5* shows that the global minimum most closely resembled the crystal structure of $[Fe(L1)_3]$ [19]. The largest deviation of the bond length of the coordinative bonds observed between

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[7]) *N,N′*-Bis(2-hydroxybenzyl)-*N,N′*-ethylenedi(2-aminoacetic acid).

Table 5. *Comparison of the Calculated and Experimental Octahedral Bond Angles of [Fe(tben)]*

Bond angle	Constraint [°]	Model [°]	Crystal [°]	Difference [°]
O(1)–Fe–O(3)	180 ± 5	172.6	177.8	5.2
O(2)–Fe–N(2)	180 ± 5	170.3	167.0	3.3
O(3)–Fe–N(1)	180 ± 5	170.5	167.5	3.0
O(1)–Fe–O(2)	90 ± 5	93.6	95.2	1.6
O(1)–Fe–N(1)	90 ± 5	85.1	86.9	1.8
O(1)–Fe–N(2)	90 ± 5	89.8	91.9	2.1
O(1)–Fe–O(4)	90 ± 5	91.2	90.3	1.9
O(2)–Fe–N(1)	90 ± 5	86.5	88.8	2.3
O(2)–Fe–O(3)	90 ± 5	91.1	85.7	4.4
O(2)–Fe–O(4)	90 ± 5	102.4	103.6	1.2
N(1)–Fe–O(3)	90 ± 5	89.5	91.1	1.6
N(1)–Fe–N(2)	90 ± 5	84.7	80.7	4.0
O(3)–Fe–N(2)	90 ± 5	84.7	86.9	2.2
O(3)–Fe–O(4)	90 ± 5	93.3	91.5	1.8
N(2)–Fe–O(4)	90 ± 5	86.6	87.2	0.6

Table 6. *Comparison of the Calculated and Experimental Dihedral Angles of [Fe(tben)]*

Dihedral angle	Constraint [°]	Model [°]	Crystal [°]	Difference [°]
C–C–O(1)–Fe	0 ± 15	– 21.6	– 35.3	13.7
C–C–O(2)–Fe	0 ± 15	– 5.8	– 19.4	13.6
C–C–O(3)–Fe	0 ± 15	– 21.0	– 28.1	7.1
C–C–O(4)–Fe	0 ± 15	– 2.6	3.0	5.6
C–C–N(1)–Fe	0 ± 15	38.9	39.9	1.0

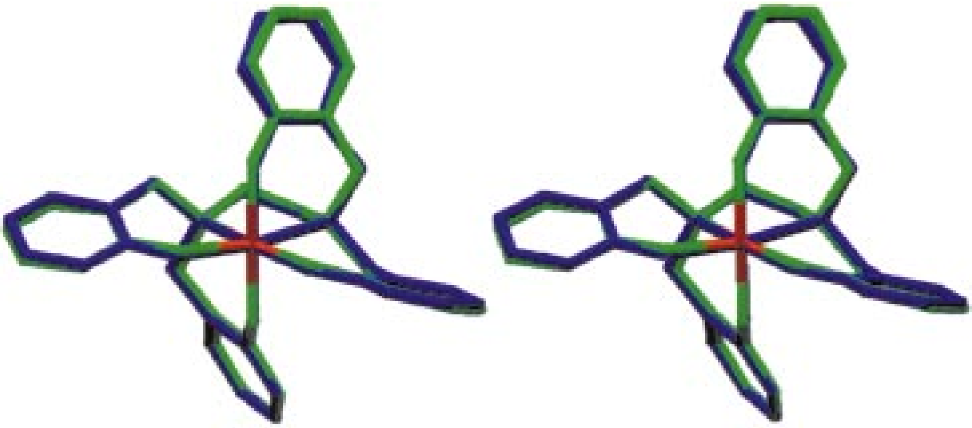

Fig. 3. *Relaxed stereoview of the crystal structure of [Fe(tben)]* (green), *superimposed on the modeled structure* (dark blue)

the crystal structure and the model was 0.008 Å or 0.4% of the average bond. The differences between the bond angles and the dihedral angles are only slightly bigger than in the former model.

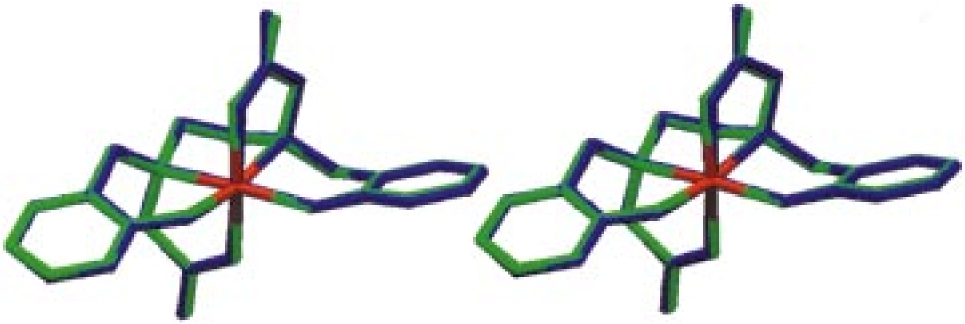

Fig. 4. *Relaxed stereoview of the crystal structure of [Fe(hbed)]* (green), *superimposed on the modeled structure* (dark blue)

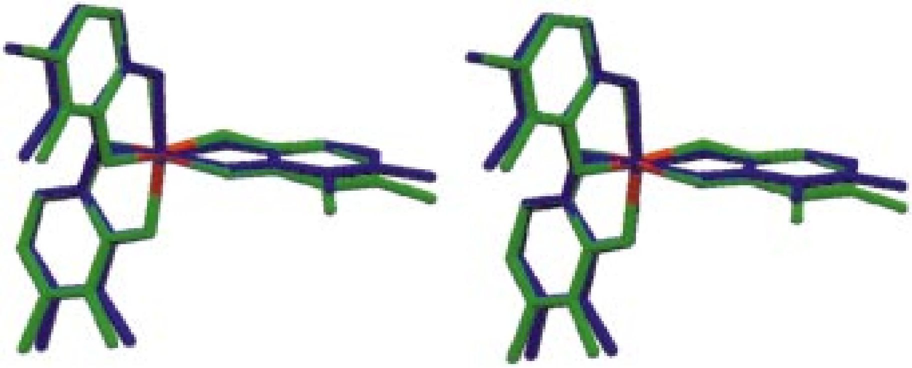

Fig. 5. *Relaxed stereoview of the superimposition of the modeled complex* (dark blue) *on the crystal structure of the iron complex with three molecules of bidentate L1* (**3**) (green)

The deformations from the ideal octahedral geometry are larger in the X-ray structure than in the calculated model. This may indicate that the chosen angular constraints are too tight, or it may be due to neglect of influences of the lattice packing forces, solvation, and counter ions. Possible extensions of the model to comprise solvation effect and maybe even lattice packing forces have never been explored, because the results obtained with this method were satisfactory for the application in designing new iron chelators. No coordination atoms other than O- and N-atoms have been explored, because the chances are minimal to find strong and selective ligands for Fe^{III} with chelators, containing S- or P-atom as coordinating atoms.

Conclusions. – A simple but rather versatile method has been elaborated and evaluated by comparison with available crystal structures of iron complexes. It allows the computation of geometries of Fe^{III} complexes at a reasonable computational expense. The method has been used for the *de novo* design of new Fe^{III} chelators, as well as to rationalize sometimes even unexpected effects observed with several iron chelators. It has also been applied for the generation of a working hypothesis for the Fe^{III}-desferal complex, which has not yet been crystallized.

The method is based on partial atomic charges obtained with *ab initio* calculations and their interaction in an empirically derived molecular-mechanics force field. The strength of this approach is that it allows the calculation and geometry prediction of a variety of ligands, and that it models the variety of bond lengths and angles often encountered in high-spin Fe^{III} complexes. Both of these properties cannot easily be reproduced with pure molecular-mechanics models, based on the constriction of the coordination bond length.

Experimental Part

All calculations were performed on *Silicon Graphics Onyx*, *Power Challenge*, and *Indy*. During the course of the elaboration of the method, we used version 3.5 up to 5.5 of MacroModel [20] and the AMBER* force field [15] for all molecular-mechanics calculations. The *ab initio* geometries and charges were calculated at 6-31G** level with versions 90 up to 94 of Gaussian [21] with the *Merz-Kollman-Singh* extension [13] (POP = MK).

Depending on the flexibility of the molecule, between 10 and 10000 conformations were generated according to the standard Monte Carlo method in MacroModel [21] and minimized with TNCG [14] or with PRCG [16], usually with the default number of minimization steps. The standard force-field charges of AMBER* [15] were used as partial atomic charges for the conformational analysis of the ligands, whereas the geometries of the complexes were calculated with the charges derived from the *ab initio* calculations. Even for complexes with a net charge, the counter ions were neglected in all calculations.

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