Design and Molecular Mechanics Calculations of New Iron Chelates

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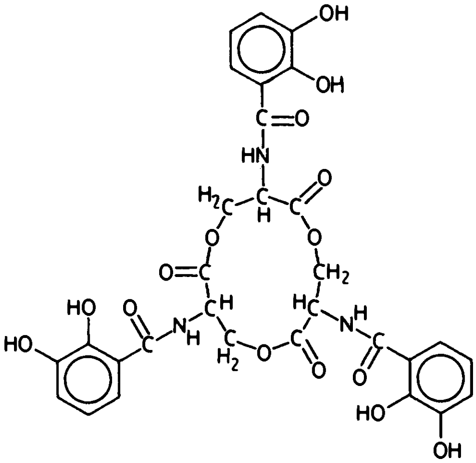
Empirical force field calculations are described with new ligands AP*n*, having two carboxylic acids and two pyrocatechol functions and forming octahedral chelates with ferric ion. The design of the ligands is described with reference to other siderophores. New parameters for treating Fe^{III} are derived from spectroscopic data and are used to complement Allinger MM2 parameters. The calculated strain energies in the series AP*n* show optimum stability of the chelate with a length of the polymethylene spacer corresponding to $n = 4$. Distortions in the octahedron are consistent with similar variations in X-ray structure. The *threo* configuration of one of the four geometrical isomers is preferred for the AP4 iron chelates.

Iron is essential in plants where a lack of the element causes ferric chlorosis,[1] and in human where an excess is toxic but where a deficiency causes anaemia.[2] Iron carriers (siderophores) are organic ligands produced by micro-organisms able to complex and transport Fe^{III} in order to establish an appropriate concentration level of the element.[3] Synthetic iron chelates already reported have been designed according to two procedures: (*a*) the biomimetic method where the molecules are derived from the structure of natural siderophores like enterobactin; and (*b*) the 'homomorph' method where the ligands have been made by positioning appropriate functional groups in given positions of an organic framework. So far the two procedures have been mostly qualitative with no calculations of the energy of the iron chelate obtained. It is the purpose of this paper to obtain quantitative data by molecular mechanics calculations on the conformations and associated energies of new iron chelates.

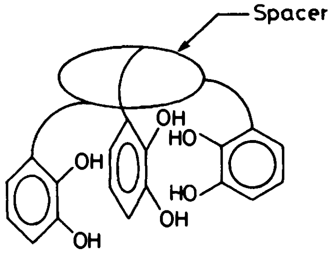
Enterobactin (**1a**), a naturally occurring iron-complexing agent, has long given the best complex constant with Fe^{3+}.[4-6] In order to improve on the chemical stability and the complexing ability of enterobactin, other ligands have been designed and synthetised.[7] Worthy of note are ligands like Cycam (**1b**),[8] Mecam (**1c**),[9] and Trencam (**1d**)[10] synthesised by Raymond *et al.*, and more recently, related macrocyclic ligands made by Vögtle *et al.*[11] All these ligands have in common three catechol units bonded onto a spacer of variable chemical structure and geometry.

Several iron chelates are presently used in agriculture for solving the problem of iron chlorosis caused by the lack of iron in plants.[1] The ligands used for this purpose are mostly EDTA [ethylenediaminetetra-acetic acid; (**2a**)] and derivatives like DTPA [diethylenetriaminepenta-acetic acid; (**2b**)], EDTA–OH [ethylenediaminetriacetic acid–hydroxy; (**2c**)], and EDDHA [ethylenediaminedi(*ortho*hydroxyphenyl) acid; (**2d**)].

It appears that enterobactin and derived ligands, or EDTA and derivatives, display the same complexing behaviour, *i.e.*, they place six heteroatoms around iron(III) at the vertices of an octahedron (or slightly distorted octahedron). With these chemical and geometrical characteristics in mind we have undertaken the synthesis of new chelating agents designed for placing in the right positions of an octahedron six oxygen atoms, provided by two catechol and two carboxy functional groups (Figure 3). We have termed these molecules AP*n* (A = acid; P = pyrocatechol; *n* = the number of methylene units) and we have undertaken their synthesis according to the Scheme.[12] The polymethylene spacer was introduced for finding the best fit between the structure of the organic ligand and the framework of the octahedron around iron(III) (Figure 4).



(**1a**)

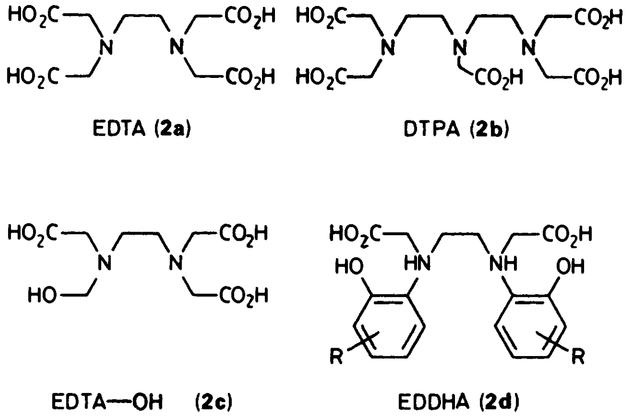


(**1b - d**)

Figure 1. Enterobactin (**1a**) and related synthetic ligands (**1b–d**).

The 'molecular model' approach which we first used was clearly an oversimplification because, as usual, the exact fitting often needed molecular distortions that could not be estimated quantitatively. Therefore we have used molecular mechanics methods [13-16] for obtaining the geometry and associated energy of new iron chelates.

Molecular mechanics (empirical force-field) methods have been applied recently for calculating complexation constants of



EDTA (**2a**) DTPA (**2b**)

EDTA—OH (**2c**) EDDHA (**2d**)

Figure 2. EDTA and derivatives.

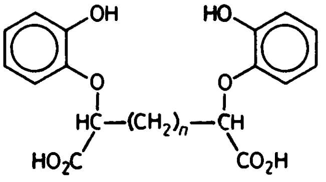


Figure 3.

alkaline, alkaline-earth and other metallic cations with organic ligands;[17–20] however to the best of our knowledge Fe^{III} has been treated only recently in one paper,[21] but all the constants used in this study are not described in detail and are not available. Consequently we first estimated and calculated the parameters related to iron; for this purpose we have made the usual assumption of all force-field methods that the strain energy of a molecule or supramolecule is the sum of classical mechanic components.

The iron-related parameters used to describe bond length deformation energy [stretching = $E_l(l)$], angle deformation energy ['Bayer strain' = $E_\theta(\theta)$], torsional eclipsing energy ['Pitzer strain' = $E_\varphi(\varphi)$] and non-bonding energy (van der Waals), are derived from spectroscopic data according to a procedure described in the Experimental section. Otherwise for carbon, hydrogen and oxygen atoms we have used the Allinger MM2 parametrization[22] and carried out the calculations with BLEMO, an adapted molecular mechanics program.[23]

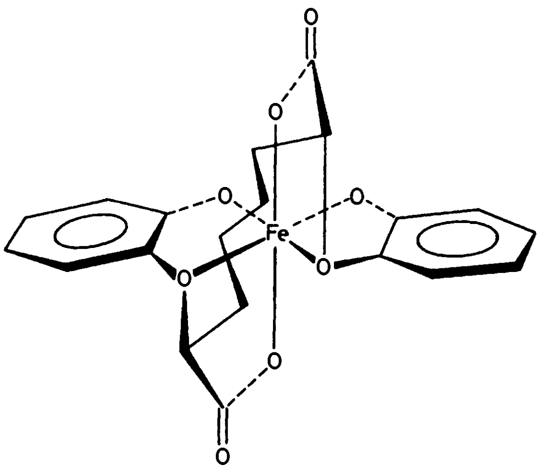
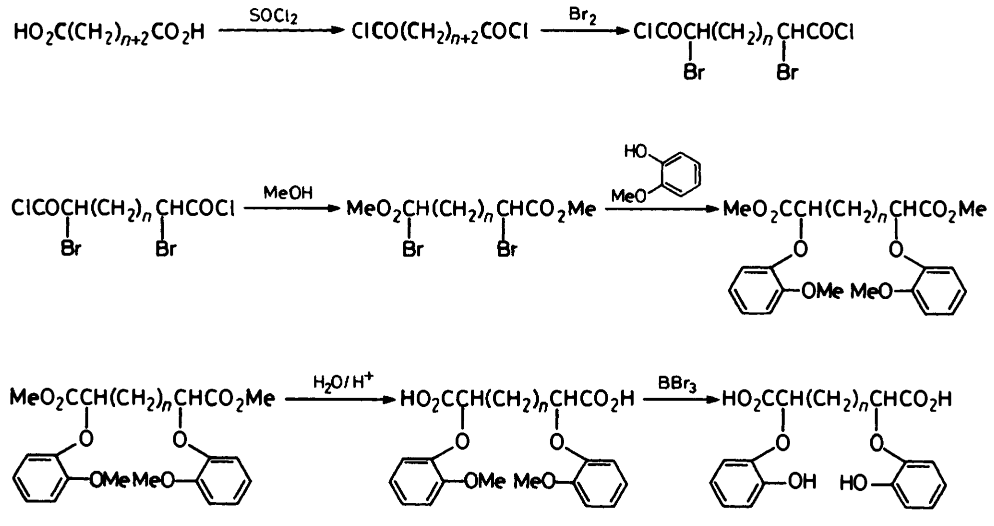


Figure 4.

The calculations commenced on the chelates depicted in Figure 4, where the two catechol units are arranged so to form a central non-distorted octahedron with iron at the centre, having six equivalent iron-oxygen bonds.* This arrangement corresponds to a geometrical isomer (I)-*threo* (see Table 2), by far the least strained among the eight possible isomers. The strain energies obtained after full relaxation are reported in Table 1 and displayed in Figure 5. They clearly show an energy minimum for $n = 4$ indicating an optimum geometry for the cavity corresponding to a spacer with four methylene units; this is shown in the ORTEP plot of Figure 6, together with a selection of bond distances and angles. The differences in energy in the AP*n* series are associated with more or less severe geometrical modifications around the iron atom. This is especially true for the bond angle (O–Fe–O) with values starting from 90° in all structures at the beginning of the calculation and ranging after relaxation from 96° (and 83°) for AP4 up to 112° for AP0. These distorted octahedrons indeed correspond to structures recently observed by X-ray for other hexadentate iron chelates.[24]



Scheme.

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* We have considered three types of Fe–O interactions; (*a*) one for Fe–O(carboxylic acid), (*b*) one for Fe–O(aryl ether), and (*c*) one for Fe–O(aryl hydroxy); the treatments are equivalent (with different parameters) for (*a*) and (*c*), but the treatment of (*b*) involves an electrostatic potential in place of a classic MM bond.

Table 1. Calculated strain energies of AP*n* iron chelates.

Iron chelates of:	Calc. strain energy/kcal mol$^{-1\,a}$	Iron chelates of:	Calc. strain energy/kcal mol^{-1}
AP0	65.231	AP6	55.212
AP1	62.124	AP7	57.367
AP2	58.563	AP8	58.325
AP3	54.325	AP9	63.203
AP4	49.798	AP10	66.986
AP5	53.721		

[a] 1 cal = 4.18 J.

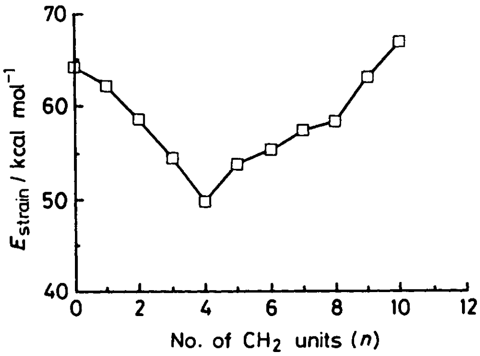

Figure 5. Strain energies *versus* the number of methylene units in the spacer.

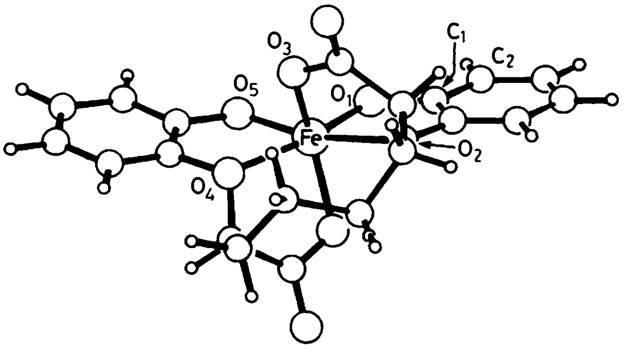

Figure 6. ORTEP plot of AP4 after energy minimization. Selected bond distances and angles are as follows: Fe–O(1), 1.92; Fe–O(2), 2.13; Fe–O(3), 1.96; O(1)–O(2), 2.58 Å; O(1)–Fe–O(2), 78.91; O(1)–Fe–O(3), 115.87; O(1)–Fe–O(4), 166.56; O(2)–Fe–O(5), 167.49; Fe–O(1)–C(1)–C(2), 9.53°.

A careful examination of the possible isomers showed that all chelates existed as four geometrical isomers (**I**)–(**IV**) (Table 2), each of them being made with an *erythro* or a *threo* form of the ligand (as the two carbons bearing the carboxy and the catechol are asymmetric). We have made a minimization for each isomer in the case of AP4 for finding the more stable complex. The values recorded in Table 2 show a close similarity between geometries (**I**) and (**IV**), with a lower energy for the *threo* configuration in each case. The more stable isomer is therefore the (**I**)-*threo* of AP4.

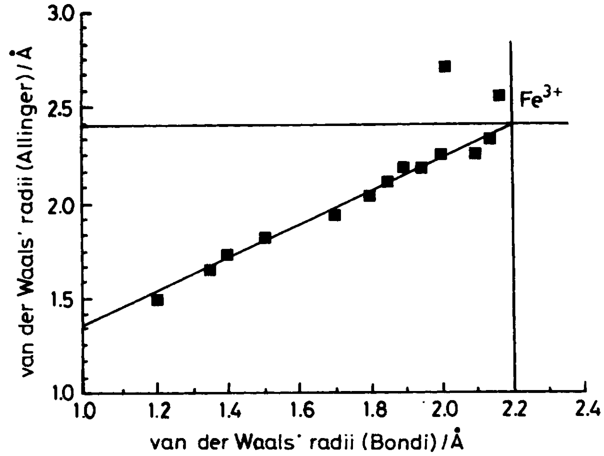

Figure 7. Van der Waals' radii from Allinger *versus* van der Waals' radii from Bondi (ref. 29).

In order to assess the usefulness of the iron parameters associated with the MM procedure described in this study * we have calculated the geometry of the iron complex of a macrobicyclic sequestering agent (bicapped trencam) and obtained a very good correlation with the X-ray geometry described recently by Raymond *et al.*[24] We plan to extend these calculations to other macrocyclic iron chelates.

To conclude, we have extended to iron chelates the force-field calculations already reported for other cation–ligand complexes; the results are consistent with previous structural data on siderophores. Physico–chemical complexation data in the series of AP*n* will allow us to check the calculations described in this paper. The method described in this article helped us in tailoring new siderophores whose syntheses are in progress. We hope that the results reported in this paper will encourage further force-field calculations of iron and other high-valent metal chelates.

Experimental

Calculations were carried out on a HP 9000-825 computer. The structures were viewed with an ORTEP program. The molecular mechanics BLEMO program[23,25] is written in FORTRAN 77, and accepts molecules with 135 atoms. It is adapted to be used easily by non-specialists. The minimization uses a step-by-step relaxation procedure carried out on internal coordinates. Allinger's 1985 parametrization[26] was used in BLEMO for the calculations, and we checked on various reference molecules that the results were identical with those of the MM2 program. The iron-related parameters were estimated as follows: for the bond length deformation energy, approximately by Hooke's law *i.e.* $E_1 = \Sigma k/2(l - l_0)^2$, we have taken, from X-ray data,[27] l_0 = 1.9955 Å for Fe–O; and from IR data of FeF_6,[28] k = 3,26 mdyn Å^{-1},† for Fe–O. For the angle deformation energy ('Bayer strain'), calculated by

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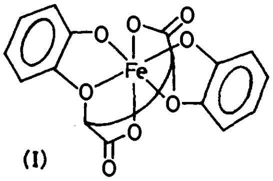
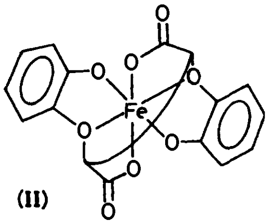
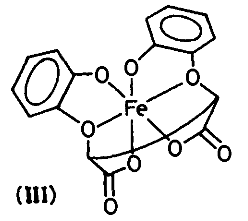
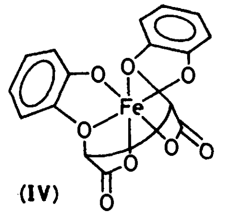
* This calculation was undertaken at the recommendation of one of the referees. The structure obtained after energy minimization is strongly distorted compared to the fully symmetrical starting octahedron, but very close to that obtained by X-ray structural analysis. The calculations of this and other related structures will be described later.

† 1 dyn = 10^{-5} N.

Table 2. Calculated strain energies after minimization of geometrical isomers of AP4 iron chelates.

Geometrical isomers of the complex	Configuration of the chelate	Calculated energy/ kcal mol^{-1}
 (I)	*threo*	49.789
	erythro	74.621
 (II)	*threo*	134.354
	erythro	162.315
 (III)	*threo*	176.056
	erythro	205.736
 (IV)	*threo*	56.681
	erythro	78.847

Hooke's law, $E_\theta = \Sigma k/2\ (\theta - \theta_0)^2$, we have taken from IR data of FeF_6,[28] k = 2,039 dyn Å rad^{-2} for FeO, and $\theta_0 = 90°$ for the initial non-distorted octahedron. For the torsional eclipsing energy ('Pitzer strain') calculated by an equation of the form $E_\varphi = v_1/2(1 + \cos\varphi) + v_2/2(1 - \cos2\varphi) + v_3/2(1 + \cos3\varphi)$, we have used for iron the v_1, v_2, and v_3 parameters of phosphorous.[22,24] For the non-bonding (van der Waals) energy, based on a 'Hill function' $E_{nb} = \varepsilon\{-C_1(r^*/r)^6 + C_2 \exp[-C_3(r/r^*)]\}$, the iron hardness ε was approximated by that of the phosphorous atom in the MM2 parametrization and distance r^* was obtained from the Fe–O length used in E_1 and from 'natural' lengths between other atoms in MM2 parametrization. r^*, the sum of the van der Waals radii of interacting atoms needed the iron(III) van der Waals radius.

When correlating the Van der Waals radii from Bondi[29] for 15 atoms, to those used by Allinger in the MM2 program, we obtained by a least squares method a correlation coefficient (r = 0.994), from which a value of 2.391 Å was extrapolated for iron(III) (Figure 7).

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Paper 9/02735A
Received 28*th June* 1989
Accepted 11*th December* 1989