Molecular Mechanics Modeling of the Cobaloximes and Reevaluation of the Parameters for Modeling of the Cobalt Corrins

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Introduction

With the development of appropriate parameters, molecular mechanics (MM) methods are useful in elucidating the structure of metal-containing molecules.[1] We[2] have described parameters for use with a modified version[3] of Allinger's MM2(87) force field[4] for modeling the cobalt corrins and used the force field to explore the relationship between the structure of alkylcobalamins and the thermolysis of the Co−C bond,[5] the structure of coenzyme B_{12}[6] and, together with nOe restraints, the structure of vitamin B_{12} in solution.[7]

The cobaloximes, compounds containing the Co(III) bis-(dimethylglyoximato) moiety, $Co(DH)_2$,[8] in which Co(III) is coordinated in the equatorial plane by four N-donors from the two monoanionic ligands and with two ligands occupying the two axial coordination sites, are of interest not only because of their rich coordination chemistry, but also because of the parallels between the properties of their organometallic complexes and the alkylcobalamins.[9] As an extension of our work on modeling of metal-containing systems, we have undertaken the derivation of the force field parameters for modeling typical nonorganometallic and organometallic cobaloximes. We have also investigated the feasibility of transferring the parameters

developed for modeling the Co−C bond and the Co−C−C angle in alkylcobaloximes to the force field for the cobalamins since relatively few alkylcobalamin structures are available for parameter development.

Since our original description of the force field for the alkylcobalamins[2] we have made increasing use of the version of MM2 referred to as MM+ available in the HYPERCHEM suite of programs.[10] This has enabled us to perform molecular dynamics (MD) and simulated annealing (SA) calculations, which we have found invaluable in modeling the cobalt corrins; the possibility exists of performing Langevin dynamics and using the Monte Carlo algorithm to sample conformational space; very large numbers of atoms can be handled; and a graphics interface provides immediate visualization of the results.

However, MM+ and MM2 treat coordination compounds differently. In MM+, like a number of other MM codes such as MM3(96),[11] Comba's MOMEC,[12] and that of Snow,[13] the coordination sphere of the metal is handled by taking into account 1,3-van der Waals interactions between donor atoms bonded to the metal (usually subsumed into angle bending terms in MM force fields), and L−M−L angle bending and X−L−M−L dihedral (L = ligand donor atom, X = any other atom) potentials are specifically excluded. Hay[14] has described a novel handling of MM2 to achieve the same effect while Ferguson and Raber,[15] have modified MM2 to the same end. This approach recognizes that metal−ligand interactions are relatively "soft" and allows for deformation of the coordination sphere in response to the metal's environment. MM2, which was not originally parametrized for metal ions, will treat a metal ion as it would treat any other atom. In situations where the complexes have a well-defined geometry, the formalism where L−M−L angles and X−L−M−L dihedrals are specifically taken into account works very well, as is evidenced by the successful modeling of many metal ions with a variety of geometries.[16]

The use of the parameters for the cobalt corrins[2] with the functional formalism of MM+ (no MM+ parameters were used) has a small, but significant, affect on the ability of the force field to reproduce the structures of the cobalt corrins to a satisfactory level of precision (which we have taken to be bond

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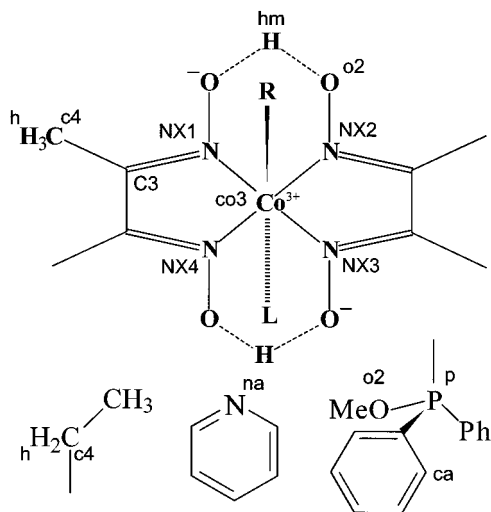
Figure 1. Generalized structure of the cobaloximes and definition of atom types used in the molecular modeling.

lengths to within 0.01 Å and bond angles and torsions to within better than 3° and 5°, respectively, of the crystallographic means). We have therefore revised the parameters for modeling the cobalamins with MM+. These modifications have been used in our most recent work[7] but not in our original investigation on the structure of the alkylcobalamins.[5,6] Revised results for the latter are presented here.

Methods

A search of the Cambridge Structural Database (CSD) was undertaken (October, 1995) to update the statistical information available[9] on the structure of the cobaloximes. Structures with reported *R* factors >10%, with obvious disorder, and with the metal in other than the +3 oxidation state were discarded. The resulting set of 146 structures was manually subdivided into organometallic and nonorganometallic structure sets, and the statistics on the bond lengths, bond angles, and torsional angles of interest were determined. The results are given in Table S1 of the Supporting Information.

All MM calculations were performed with MM+[10] using a 200 MHz PC. Atom types defined for the cobaloximes are shown in Figure 1. Geometry optimizations were performed using a conjugate-gradient procedure with a convergence criterion of 0.01 kcal mol^{-1} Å^{-1} rmsd in the gradient. To help avoid local minima, all atomic coordinates were subjected to a random <0.05 Å perturbation and the structure was reminimized after convergence. This was repeated until there was no further significant decrease in the molecular strain energy. Alternatively, a molecular dynamics simulation (heat from 300 to 1000 K over 2 ps; 2−5 ps run at 1000 K; simulated annealing to 300 K over 10 ps; full energy minimization) was used to overcome local minima.

Parametrization started by setting the strain-free bond length (l_0) and bond angle (θ_0) values to the crystallographically observed means (Table S1). Initial values of the force constants for all potential energy functions were those used previously.[2] Angle bending terms of the type X−M−X and torsional terms involving the metal ion, X−M−X−X, were treated as simple harmonic potentials. The values in MM2 were used for all other parameters.

A trial cobaloxime structure with Cl$^-$ occupying the two axial sites was used to develop a generalized force field for nonorganometallic cobaloximes. The structural parameters were compared with the crystallographic means, and the force field parameters were adjusted on a trial-and-error basis until a best fit to the average crystallographic values was obtained. These parameters were used as a starting point for the development of parameters for organometallic structures, the trial structure in this case containing Me and PPh$_3$ as axial ligands.

Optimum parameters for the Co−P bond length and Co−P−C and Co−P−O bond angles were determined for structures with R = Me by systematically varying l_o, k_s, θ_o, and k_b individually, with all other

parameters fixed, until a set of parameters was found which gave the smallest rmsd between the modeled and the crystallographic structures. A similar approach was adopted for the Co−N bond and Co−N−C angle for modeling Co-bound pyridine, with the starting parameters those previously used for modeling iron porphyrin−pyridine structures.[17a] A series of alkylcobaloximes ([CoDH$_2$](R)(L), with the alkyl trans to a phosphine or py) was used for developing parameters for the Co−C bond and the Co−C−C angle. The parameters previously used[2] for the Co−C−H angle were used unmodified. The structures used were R = Me, L = PMe$_3$;[18] R = Me, L = P(C$_6$H$_{11}$)$_3$;[18] R = CH$_2$C(Me)$_3$, L = PPh$_3$;[19] R = C$_2$H$_5$, L = PPh$_3$;[20] R = CH(Me)(Et), L = PPh$_3$;[20] R = Me, L = P(OMe)$_2$Ph;[21] R = Me, L = P(OMe)Ph$_2$;[21] R = i-C$_3$H$_7$, L = PPh$_3$;[22] R = Me, L = PPh$_3$;[23] R = Me, L = py;[24] R = CH$_2$C(Me)$_3$, L = py;[25] and R = i-C$_3$H$_7$, L = py.[26]

The protons in the O−H−O bridges of the cobaloximes are usually (but not always) attached to the two separate glyoxime moieties.[9] Because of the positional disorder of the equatorial ligands in the crystal, only the average structure, with the hydrogen atom nearly in the middle of the bridge, is observed in diffraction experiments.[9,27] We modeled the bridge system with the H atom in the middle of the two oxygen atoms; this required particular parameters, including a decrease in the van der Waals radius of the bridging H from 1.5 to 1.2 Å to maintain it close to the mean equatorial plane. All bond dipole moments were set to zero, as we[3,17] and others[28] have done previously in modeling metalloporphyrins[3,17,28] and cobalt corrins.[2]

Results and Discussion

Modeling the Cobaloximes. The modeling of the coordination sphere of Co(III) in the cobaloximes proved unsatisfactory when using only 1,3-van der Waals interactions, with angles and torsions often differing by more than 4 and 7°, respectively, from the crystallographic means. We therefore applied an additional function, a simple harmonic potential of the general form $U = k_p (p - p_0)^2$ where the parameter p is either a L−M−L angle or an X−L−M−L dihedral and k_p is a force constant. The smallest possible values of k_p were used to prevent over-rigidity as cobaloximes are known to be quite flexible.[9] Simple harmonic potentials are used in many well-established force fields to model valence angles,[29] and, in the neighborhood of the turning point, a quadratic function is a

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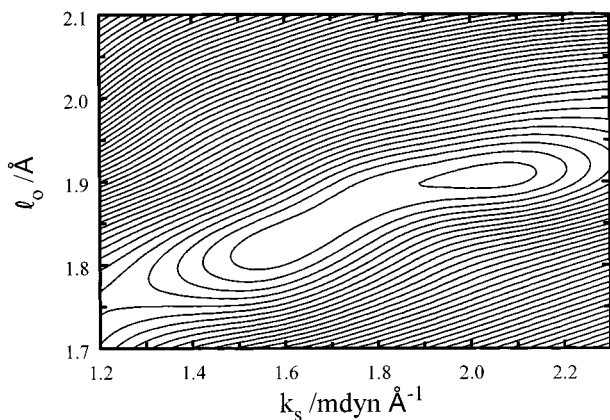
Figure 2. Contour plot of the rmsd between the values of the Co–C bond length in alkylcobaloximes modeled by MM methods and observed crystallographically. The minimum rmsd occurs at $l_o = 1.905$ Å and $k_s = 2.03$ mdyn Å^{-1}.

reasonable approximation to the cosine function used to model dihedrals. The optimized force field parameters for nonorganometallic and organometallic cobaloximes are given in Tables S4–S15 of the Supporting Information. Figure 2 shows an example of the contour plot from a grid search for the optimum Co–C bond length.

There is reasonable agreement between the crystallographic mean bond lengths and bond angles for the equatorial glyoxime moieties and those obtained from the MM modeling (Table S1); bond lengths are reproduced to better than 0.01 Å and bond angles and torsion angles to better than 2 and 3°, respectively. In the case of the axial bond lengths of alkylcobaloximes, the agreement is poorer. This is almost certainly a consequence of the small sample size (Table S2); there are only 12 structures with Co–C bonds: nine with Co–P bonds and three with Co–N(py) bonds. The rmsd is a reasonable 0.02 Å for Co–C and 0.015 Å for Co–N but is very large, 0.09 Å, for Co–P, with one structure, that of [Co(DH)$_2$(Me)(P(OMe)$_2$Ph)],[21] differing by 0.25 Å. Leaving out this structure decreases the rmsd to 0.06 Å. Only the availability of additional structures of this type will permit a decision whether this is an outlier or whether there is a fundamental deficiency in the modeling.

For a force field to be useful it must reproduce a range of observed structural effects in novel compounds of the series for which it is designed. We investigated the ability of the force field to reproduce the structure of an alkylcobaloxime recently reported—and hence not included in the statistical survey of the CSD—[Co(DH)$_2$(n-Pr)(H$_2$O)], as well as the structure of its inclusion complex with α-cyclodextrin (α-cd). The molecular modeling of [Co(DH)$_2$(n-Pr)(H$_2$O)] started from the crystal structure coordinates, proceeded by a molecular dynamics/ simulated annealing (MD/SA) procedure, and a full geometry optimization. An MD/SA procedure failed in the case of the cobaloxime–α-cd structure as the two molecules simply moved apart. The modeling of this complex was therefore started from the crystal structure coordinates; fifty random structures were generated by changing every atomic coordinate of each atom by between −0.5 and 0.5 Å using a random number generator,
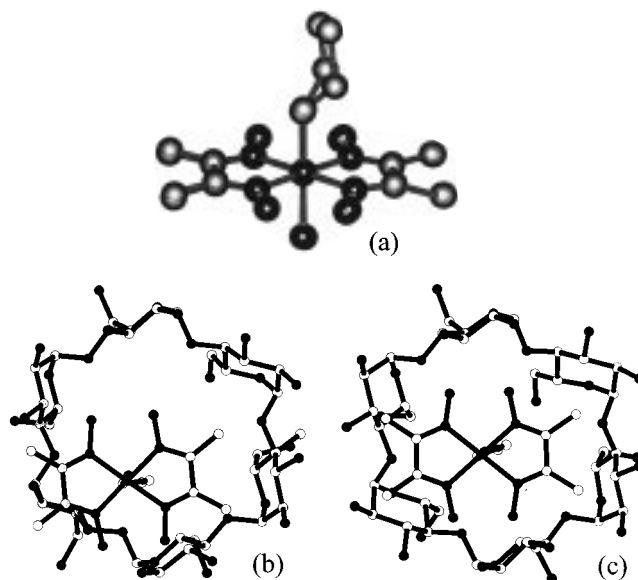
Figure 3. (a) Overlay of the crystallographic[31] and molecular mechanics structure of [Co(DH)$_2$(n-Pr)(H$_2$O)]. Crystallographic[31] (b) and molecular mechanics (c) structure of [Co(DH)$_2$(n-Pr)(H$_2$O)]·α-cd.

each structure was energy minimized and the lowest energy structure found was chosen. A comparison of the crystal and MM structures of [Co(DH)$_2$(n-Pr)(H$_2$O)] and its α-cd inclusion complex is shown in Figure 3 and detailed in Table S3. The bond angles and bond lengths of the structures are satisfactorily reproduced, except for the C$_1$–C$_2$ bond length in the coordinated alkyl group. The MM value (1.536 Å) is close to the value expected for alkanes, whereas the crystallographically observed C$_1$–C$_2$ bond length is considerably shorter (1.237(12)).

Bond shortening of the C$_1$–C$_2$ bond length has been attributed to hyperconjugation in some organocobaloximes such as complexes of the type [Co(DH)$_2$(CF$_3$CH$_2$)L].[9,20,32] There is structural evidence for and against these bond shortening effects. In addition to [Co(DH)$_2$(i-Pr)(OH$_2$)], the C$_1$–C$_2$ bond is also short in [Co(DH)$_2$(Et)(PPh$_3$)] (1.317 Å),[20] marginally shorter in [Co(DH)$_2$(CH(Me)Et))(PPh$_3$)] (1.449 Å for C-Et; 1.506 Å for C-Me),[20] normal in [Co(DH)$_2$(CH$_2$C(Me)$_3$)] (1.555 Å),[19] and shorter and longer in [Co(DH)$_2$(i-C$_3$H$_7$)] (1.58 and 1.49 Å).[22] In the alkylcobalamins the structural evidence is also inconclusive. One molecule in the unit cell in the X-ray structure of AdoCbl has a C$_1$–C$_2$ bond length of 1.472 Å, but the other a bond length of 1.562 Å;[33] and in the (R)- and (S)-2,3-dihydroxypropylcobalamins these bonds lengths are 1.47 and 1.68 Å, respectively.[34] We view the issue as unresolved and have therefore treated the C$_1$–C$_2$ bond length with the standard MM2(87) parameters for alkanes.

The "cobaloxime angle" α between the two DH units is usually close to zero,[9] although a sterically demanding ligand in one of the equatorial positions can increase the angle significantly.[35] In [Co(DH)$_2$(n-Pr)(H$_2$O)], α = 1.6°, with the atoms in each glyoxime moiety virtually coplanar; in the MM structure, α = 2.6°, and the atoms in each glyoxime unit are virtually coplanar. Inclusion of the alkylcobaloxime into α-cd

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causes a folding of the cobaloxime toward axial H_2O, with α = 10.4 and 12.1° in the crystal structure and the MM structure, respectively; thus the cobaloxime equatorial plane is appropriately flexible in the model. The orientation of the *n*-Pr ligand relative to the equatorial moiety is not reproduced; this is not surprising since the alkyl ligand is free to rotate relative to the DH units, and its orientation could be very readily influenced by packing forces in the solid state.

A significant difference between the crystal and MM structures of $[Co(DH)_2(n\text{-}Pr)(H_2O)]\cdot\alpha$-cd is the position of the cobaloxime moiety relative to the cyclodextrin. In the crystal structure, the cobaloxime is close to one "wall" of the cyclodextrin and hydrogen bonding between two of its oxygen atoms and three OH groups of cyclodextrin is likely,[31] and there is an extensive network of intermolecular hydrogen bonds. The force field used does not take hydrogen bonding into account, and the cobaloxime is located near the center of the cyclodextrin cavity.

Modifications to the Force Field for the Cobalt Corrins. Use of the parameters specifically developed for the cobalamins[2] with MM+ reproduces the structure of the cobalamins equally as well as MM2(87), with the exception of the coordination sphere of the metal ion and other features of the structure consequent on this such as the corrin fold angle.[36] For example, the rmsd's of bond angles of the form L–Co–L between the crystal structures of AdoCbl,[33] H_2OCbl^+,[37a] and MeCbl[37bc], and the MM structures in which the coordination sphere is modeled only with 1,3-van der Waals interactions are 4.0, 3.7 and 9.0°, respectively; the rmsd's for dihedrals of the form L–Co–L–X are 6.6, 9.1, and 8.7°, respectively. When harmonic potentials are added (Table S21), these decrease, respectively, to 1.7, 1.2, and 1.2° and to 4.1, 2.9, and 2.0°. A detailed comparison is given in Table S22. All the force field parameters for the cobalt corrins are given in Tables S16–S21.

The parameters developed for the Co–C bond and the Co–C–C bond angle for the cobaloximes were transferred to the MM+ cobalamin force field, and the ability of the force field to reproduce the structures of AdoCbl,[33] AdePrCbl,[38] MeCbl,[37b]

(*R*)- and (*S*)-2,3-DHPrCbl,[34] and CF_3Cbl[39] was investigated (Table S23). The new parameters are about as effective as the previous parameters at reproducing these features of the structure of the alkylcobalamins (rmsd = 0.03 and 0.03 Å and 3 and 4°, with the previous and the present parameters, respectively).

We have repeated the determination of the MM structures of four alkylcobalamins (MeCbl, AdoCbl, BzCbl, and NpCbl) as previously reported.[5] We find (Table S24) a marginal decrease in the population-weighted Co–C bond lengths for MeCbl and NpCbl and a slight increase for AdoCbl and BzCbl; the Co–C–C bond angles have increased marginally for AdoCbl and BzCbl and decreased marginally for NpCbl. A plot (Figure S1) of the Co–C bond dissociation energies against the population-weighted Co–C bond length and Co–C–X (X = H for MeCbl; X = C for AdoCbl, BzCbl, and NpCbl) produces the inverse relationships we had previously noted. Hence the main conclusions previously reached[5] concerning the probable importance of these structural parameters in controlling the Co–C bond dissociation energy remain unchanged.

Supporting Information Available: Table S1, crystallographic and molecular modeling mean bond lengths and angles of the cobaloximes; Table S2, comparison of crystallographic and MM-modeled axial bond lengths of alkylcobaloximes; Table S3, comparison of selected structural parameters in the solid state and MM-modeled structure of $[Co(DH)_2$-$(n\text{-}Pr)(H_2O)]$ and its α-cd complex; Tables S4–S15, MM parameters for organometallic and nonorganometallic cobaloximes; Tables S16–S21, MM parameters for modeling cobalt corrins; Table S22, comparison of some bond angles and torsional angles involving cobalt in the crystal strucctures of AdoCbl, H_2OCbl^+, and MeCbl with MM structures produced with and without restraints; Table S23, comparison of crystallographically observed and MM energy-minimized Co–C bond lengths and Co–C–C and Co–C–H bond angles using MM2-(87) and MM+; Table S24, structural parameters for alkylcobalamins determined by MM methods; Figure S1, dependence of the bond dissociation enthalpy of alkylcobalamins on the population-weighted Co–C bond length and Co–C–X (X = H, C) bond angle; (43 pages). Ordering information is given on any current masthead page.

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(36) The angle between the mean planes of N21, C4, C5, C6, N22, C9, and C10, and N24, C16, C15, C14, N23, C11, and C10, respectively.

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