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Solution Structures of Coordination Compounds

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Structures of small organic and coordination compounds may be calculated rather efficiently and accurately with molecular mechanics. Two major, and still largely unsolved, problems of this method are: (i) the environment of the molecules is usually not included, although with a considerable effort this is basically possible; and (ii) it is not possible with certainty to find the global energy minimum with a general method, a problem that is especially annoying for relatively large systems (more than a few hundred conformers), where all minima may not realistically be screened separately. One possibility addressing both problems consists of combining the computation of structures with experimental results related to the output data of molecular mechanics calculations (nuclear coordinates, strain energies and/or vibrational frequencies). Examples of this approach presented and discussed here indicate that relatively accurate solution structures may be obtained via combinations of molecular mechanics calculations with solution spectra or experimentally determined isomer distributions.

Key Words: *molecular mechanics, molecular modelling, spectroscopy, solution structure, global energy minimum, coordination compounds*

INTRODUCTION

With the development of modern crystallography that has made X-ray and, to a lesser extent, neutron diffraction studies widely

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accessible, a new rule has emerged that compels every chemist to prove the molecular structure of a new compound, be it the result of an elaborate synthesis or the isolation of a challenging natural product, by a crystal structure. Only if the new products in hand are very similar to already existing ones (and therefore structurally not much of a challenge), if they do not crystallise (and therefore are an annoyance) or if they end up in the hands of a dedicated spectroscopist might they escape a study by X-ray or neutron diffraction. Apart from still possible (with increasingly sophisticated software more and more disappearing) operator errors and from inaccuracies due to poor quality of the crystals or the large size of the molecule, crystal structures are often believed to yield unambiguously corrected answers.

The fact that no other method can measure structures with the accuracy and detail of X-ray or neutron diffraction studies often leads one to forget two facts: (i) crystal structures represent only the product crystallised out of a solution (and this might not be the most abundant or important but the least soluble part of a mixture), and (ii) the crystal structure might not be similar to the solution structure, a fact that has some importance with labile compounds, e.g., complexes of labile metal ions. In view of the fact that the behaviour of compounds in solution is of particular interest in many cases (preparative chemistry, homogeneous catalysis, biological systems), these deficiencies of crystal structures are a large drawback and of some concern.

Other direct methods for structural characterisation generally involve spectroscopic techniques that may involve measurements in solution. Among these methods, EXAFS and NMR spectroscopy (NOE experiments) are the two techniques that yield data that are, compared with other techniques, most directly related to nuclear coordinates. However, the information obtainable is by no means as complete and as easily and unambiguously interpretable as X-ray data.

Another way to obtain information on nuclear coordinates of a compound is to compute the structure. A number of techniques are available, ranging from ab initio calculations to semi-empirical MO techniques, molecular mechanics (MM) and purely geometrical models. There is a large difference between these techniques in terms of their theoretical basis, rigor and sophistication. Due

to the CPU time required for rigorous calculations it is not always the most sophisticated and scientifically most appealing technique that leads to the best result. For a number of reasons, MM calculations have attracted much attention in the area of structure optimisation. This is mainly due to the fact that the time required to compute a structure is relatively small, so that all possible geometries (conformers, isomers, etc.) can be considered, and even large molecules (proteins, polynucleotides, etc.) may be treated routinely.

The problem of any calculation is to judge the error limit and relevance of the results. The question of how accurately a computed structure agrees with the experimental results raises three additional, partly related points: (i) Does a computed structure have to be in agreement with the corresponding crystal structure? This relates to the problems discussed above and the question of whether any environmental effects have been included in the computation (see below). (ii) Why should a structure be computed when the corresponding experimental data (X-ray structure) are obtainable, known and believed? (iii) Is it possible to extrapolate from one compound to another in terms of the accuracy of a computed structure? This latter question will be briefly discussed in a short paragraph on parameterization.

In this Comment I will present an approach to refine solution structures of coordination compounds, using MM calculations and taking into account the two main problems inherent to MM, i.e., the influence of the environment with regard to the structure and strain energy, and the location of the global energy minimum. The method described is based on the observation that the structure of any compound is related to its molecular properties, i.e., to its stability, reactivity and electronic properties (e.g., spectroscopy) (see Fig. 1). If an algorithm is found that relates the (calculated) structure (various conformers) of a compound with any of these properties, then a combination of the computation of a structure with experimental data may lead to a reasonable refinement of the structure in the corresponding environment, e.g., in solution.

MOLECULAR MECHANICS

MM is widely recognised as a useful tool for the prediction and interpretation of structures and relative stabilities of coordination

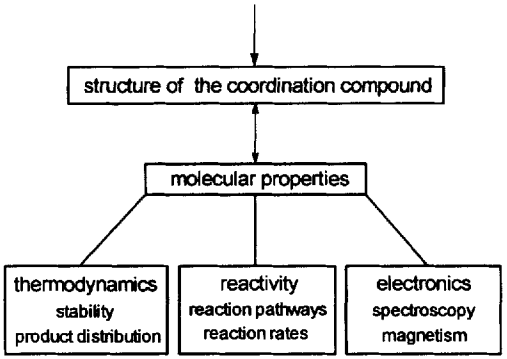

FIGURE 1 Relation between ligand structure and molecular structure of the coordination compound and molecular properties.

compounds, although the open-shell electronic structure of d-metal complexes is still a problem in the process of developing a general parameterization (see ahead). The general approach, various parameterization schemes and possible applications in coordination chemistry have been reviewed and discussed in a number of recent texts.[1-4] MM is usually discussed as a simple model describing a molecule as an assembly of atoms located at positions defined by potentials between two atoms (bonds, E_b), three atoms (valance angles, E_θ), four atoms (torsion angles, E_ϕ), van der Waals interactions between non-bonded atoms (E_{nb}) and additional terms which are occasionally used to describe electrostatic interactions, hydrogen bonding and other effects.

$$U_{\text{total}} = \Sigma(E_b + E_\theta + E_\phi + E_{nb} + \cdots) \qquad (1)$$

Minimisation of the sum of energies resulting from these potentials leads to an optimised structure (minimum on the energy surface) representing isomers and/or conformers with a given stoichiometry.

The shape of the computed energy surface and thus the accuracy of the structural and thermodynamic predictions is strongly dependent on the functional forms of the potentials used and their parameterization. These parameters (the force field) are usually based on experimental data (predominantly crystal structures) of

classes of compounds. Thus, and this is a different and more accurate view, MM is an empirical technique to compute Born–Oppenheimer surfaces. Since MM is entirely based on experimental data (recent developments[5–7] have shown that the set-up of energy functions does not need to be based on the simplistic but intuitively reasonable set of potential functions given by Eq. (1)), it is primarily limited by the set of experimental data used for the parameterization. The main point to be made here is that one should compute only structures that are similar (connectivity, electronic effects, range of induced strain) to the set of structures used for the development of the force field; i.e., in developing a "general" force field, structures varying as much as possible must be considered.

Commonly used potential energy functions and parameterization schemes (force fields), the problem of transferability of parameters sets, the relation of force field parameters to physical data and general limitations of the concept have been discussed elsewhere and will not be repeated here.[1–4] In the applications that I will discuss below, we have used the computer program MOMECPC[8] using a published force field.[9] The functional forms (Eq. (1)) used are conventional with the exception that valence angles involving the metal center are replaced by ligand–ligand repulsion (1,3-interactions)[9] or a combination of repulsion and an angle bending potential represented by a harmonic sine function, with the ratio between repulsion and harmonic sine term being tuned by the ligand field strength, thus accounting for electronic effects due to the open d-shell.[10] Generally we do not model electrostatic interactions as a separate term, and van der Waals interactions with the metal center are neglected. For reasons for and limitations of these approximations I refer the reader to the literature.[1–4]

A common problem of MM calculations is the fact that, for simplicity, usually "naked" species are computed, i.e., the environment is neglected (actually, with the generally used approach of parameterizing the force field with crystal structures, the resulting force field reflects net averaged crystal lattice effects). The computed structures of "naked" species are generally more symmetrical than expected based on selective interactions in a crystal lattice or by solvation and ion-pairing. However, interactions with

the environment often lead to only minor perturbations of the structures; i.e., depending on the quality of the force field, there is generally excellent agreement between computed structures of "naked" molecules and experimental structural parameters that are averages of symmetrically related parts of the molecule. Programs are available that allow the simulation of lattice effects and solvation. With the development of faster computers and less time-consuming algorithms, the future probably will see more studies where the possible source of error caused by the neglect of environmental effects will be removed.

Another problem inherent to MM is that, depending on the complexity of the molecule, the energy surface has an exceedingly large number of minima, and to screen them all separately becomes impractical. Although a number of algorithms aiming to solve this problem, including molecular dynamics and Monte Carlo type algorithms, e.g., involving random torsional angle search procedures, have been developed and used,[11-15] there is no general and secure way to find the global minimum. Apart from not being rigorous, all the methods used are rather time-consuming. Also, in relation to the problem of treating environmental effects, the global minimum of the "naked" molecule—if it is determined—is not necessarily identical to the most stable solution structure.

The method that I describe here involves the determination of experimental data relatable to structural properties, MM refinement of the molecular structure derived from these properties, and comparison of the experimental data with the corresponding computed parameters based on the MM structure (see also Fig. 1). Thus the method discussed involves MM in combination with an experimental technique and an algorithm relating the corresponding parameters to structural data.

MOLECULAR PROPERTIES RELATED TO STRUCTURAL PARAMETERS

Among the molecular properties related to coordination geometries which therefore might be used in combination with MM calculations are thermodynamic and kinetic properties, vibrational

frequencies, UV-vis-NIR spectra, EPR spectra, magnetic moments, NMR spectra and redox properties.

Some applications of the general approach to compute solution structures of coordination compounds based on MM and the experimental evaluation of isomer distributions, on MM optimised structures and simulated EPR spectra, and on MM in combination with angular overlap model (AOM) calculations (UV-vis-NIR and EPR parameters) will be discussed below. The computation of electron transfer rates and redox potentials based on structural parameters is presently being evaluated in our lab. IR and NMR spectroscopy have not yet been used extensively in combination with MM of coordination compounds. However, basically there is no methodological difference to corresponding applications in organic chemistry, which will be discussed now.

IR Spectroscopy

There are a number of different methods used for minimising the total strain energy of a molecule leading to its optimised structure.[4,16,17] The full matrix Newton–Raphson algorithm[18] is a minimiser that uses the curvature of the total potential energy function to optimise a structure and therefore needs comparably few cycles to find the energy minimum. However, due to the amount of information to be computed and stored, it is only of practical use for relatively small molecules (a few hundred atoms at most), and it only leads to stable configurations if the starting geometry is relatively close to an energy minimum. The information used for minimization is the Hessian matrix (second derivatives of the energy for all Cartesian coordinates x_i,y_i,z_i, $i = 1-N$, i.e., $9N^2$ matrix elements for N atoms), which effectively is the full matrix of force constants. These may be used to calculate vibrational frequencies,[18] which obviously depend on the geometry of the molecule and may therefore be used for comparison with solution experimental data in order to determine solution structures.

NMR Spectroscopy

All relevant NMR parameters, viz. chemical shifts, coupling constants and NOE effects, are dependent on the molecular geometry and may therefore be used for structural correlations. The Karplus

equation[19] defines the vicinal proton coupling constant ^3J as a function of the corresponding torsion angle ϕ leading to some information on the local geometry, which may be used for MM refinements. NOE effects are used for the refinement of solution structures, mainly in the area of proteins,[20] via the evaluation of distance geometry maps, which then may be refined and used again for the simulation of NOE spectra in the process of refinement of a solution structure. Recent successful applications of this technique have also involved a number of coordination compounds.[21–23] Chemical shifts may be calculated, e.g., with the method of individual gauge for localised orbitals (IGLO),[24,25] although in this case it remains to be demonstrated that MM structures are accurate enough to lead to reasonable predictions.

ISOMER DISTRIBUTIONS

Strain energies are widely used for the determination of conformer and isomer distributions in thermodynamic equilibrium mixtures.[2] The quality of isomer ratios, computed via partition functions using strain energies, is dependent on the force field and thus directly linked to the quality of the computed structures. With well-tuned force fields the error limits for coordination compounds are in the region of ca. 5%. The experimental determination of isomer ratios depends on quantitative spectroscopic techniques (e.g., integrals of ^{1}H-NMR spectra) or chromatography. Two out of many examples studied so far will now be discussed in some detail.

A full conformational analysis of $[Co(trab)_2]^{3+}$ (trab = butane-1,2,4-triamine, 16 conformers all together)[26] revealed that the chair–chair conformer of each of the five isomers (three for optically pure trab; A,B,C in Fig. 2) was most stable, with each skew-boat conformation leading to a loss in energy of ca. 6 kJ/mole. From the three isomers A,B,C of the cobalt(III) complexes with optically pure trab, one was not resolved with HPLC, and the two additional isomers involving racemic trab (D and E) were separated from the two peaks of the first three isomers but not resolved from each other. The ^{13}C-NMR spectra only allowed the unambiguous assignment of isomer E for symmetry reasons. However, the relative ^{13}C-NMR intensities and the integrals of the chromatograms to-

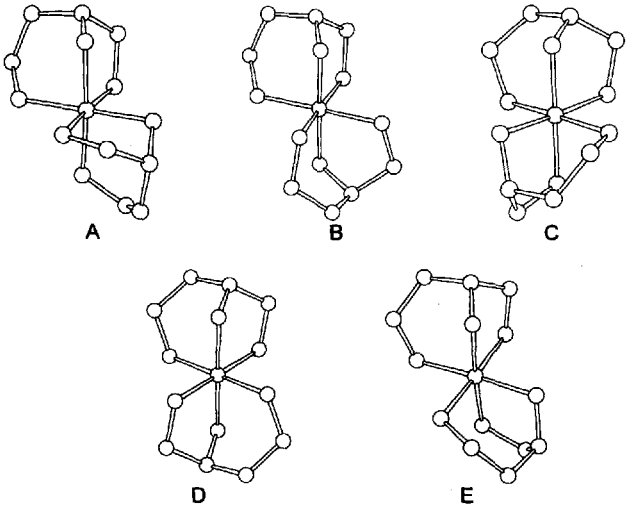

FIGURE 2 Calculated structures of the five isomers (most stable conformers) of $[Co(trab)_2]^{3+}$.

TABLE I

Calculated and experimentally determined isomer distribution of $[Co(trab)_2)]^{3+}$ (Ref. 26).

Isomer	Calc. [%]	Exp. [%]
A	21	21
B	16	15
C	16	15
D	4	4
E	43	45

gether with the calculated isomer distributions (MM) led to an unambiguous assignment of three of the five isomers (see Table I), with chromatographic peaks and ^{13}C-NMR shifts still not attributed for isomers B and C (same abundance). Isomer E with 44% was defined as the global energy minimum with other isomers up to ca. 7 kJ/mole higher in energy.

In a similar recent study the solution structure of the isomeric mixture of *cis*-diethoxybis-(1-phenylbutane-1,3-dionato)titanium-

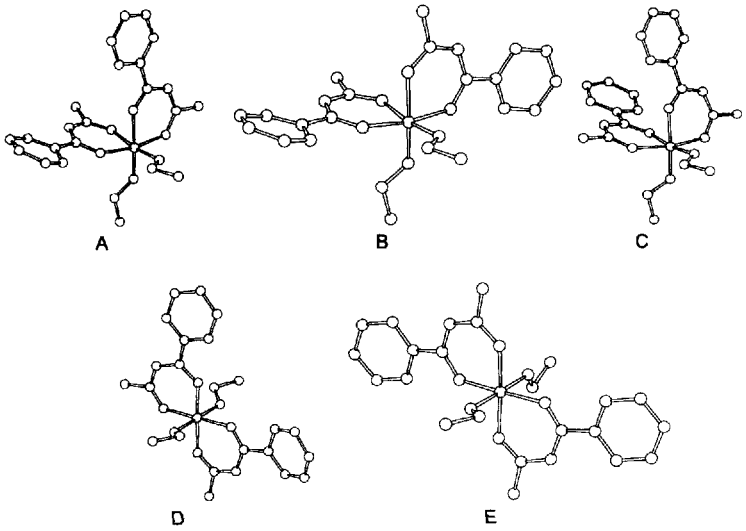

FIGURE 3 Calculated structures of the five isomers of budotitane.

(IV) (Budotitane), a promising anti-cancer drug, was evaluated (see Fig. 3).[27] The existence of three isomers was apparent from ^{1}H-NMR spectroscopy and, for symmetry reasons, they were attributed to the three *cis*-isomers A,B,C with experimentally determined abundances (not unambiguously attributable to the different species) of 60%, 21% and 19%. Determination of the ratios via strain energies led to abundances of A:57%, B:17% and C:26% (see Table II). Again, the good agreement between experimentally observed and calculated isomer ratios indicates that the calculated structures are rather accurate. The method also allowed the unambiguous assignment of the NMR resonances.

In the two examples discussed in this section, strain energies have been correlated to experimentally obtained relative stabilities. Clearly, this does not yield any *direct* structural information. However, strain energies and the corresponding optimised structures are directly related. Therefore, their quality (experiment vs. computation) is also directly related, i.e., the good agreement between calculated and experimentally determined abundances (Tables I and II) supports the quality of the calculated structures. In the two examples discussed below, spectroscopic data are used

TABLE II

Calculated and experimentally determined isomer distribution of budotitane (Ref. 27).

Isomer	Calc. [%]	Exp. [%]
A	57	60
B	17	19
C	26	21
D	0	0
E	0	0

in the process of structural refinements. In these cases, relative strain energies are not directly relevant. However, I will explicitly demonstrate in the first example that the appreciation of the relative differences of strain energies may lead to additional insight into the chemical systems discussed, and that the relative strain energies may therefore support a structural assignment. Also, conformational distributions may be relevant, and this will be demonstrated in the second example.

SOLUTION STRUCTURES OF WEAKLY COUPLED DINUCLEAR COPPER(II) COMPLEXES

The EPR spectra of weakly coupled $S = 1/2/S = 1/2$ spin systems (dipole–dipole interactions) may be simulated with the spin Hamiltonian parameters of each of the two chromophores and the four geometric parameters r,τ,ξ,η defining the orientation of the two chromophores (see Fig. 4).[28] The number of parameters involved varies from 16 (two different rhombic chromophores; parameters for line widths and exchange coupling not included) to 8 (two identical tetragonal chromophores). Even for complexes leading to well-resolved spectra, the number of variables is too large for an unambiguous structural assignment. Also, the resulting structural data only describe the relative orientation of the two g-tensors and therefore give at most some information on the relative orientation of the chromophores and thus no data related to the ligand conformation and overall shape of the molecule. Also, MM alone

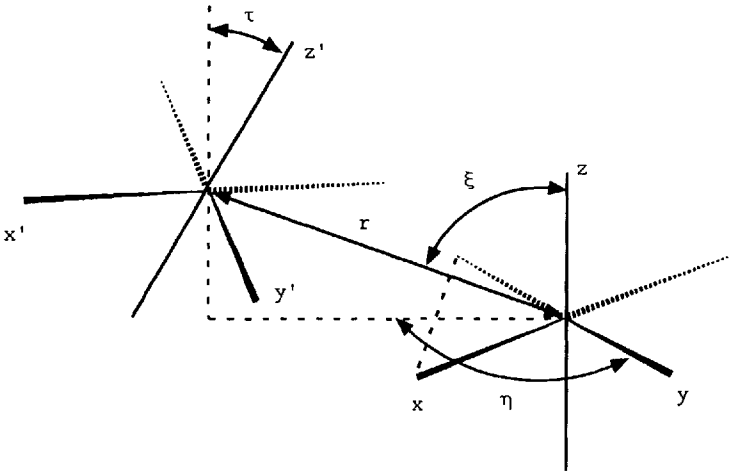

FIGURE 4 Structural parameters used in the simulation of the EPR spectra of weakly coupled dinuclear copper(II) complexes.

may not lead to an unambiguous solution. The problem here is that with the usual flexibility of dinucleating ligands the resulting number of possible conformations generally prevents the optimisation of all geometries.

A combination of the two techniques has been used to determine solution structures of weakly coupled dicopper(II) complexes.[29] After a crude simulation of the EPR spectrum (initial guesses for the g- and A-values and of the geometric parameters may be obtained from EPR spectra of related monomeric compounds and from some knowledge of the chemical systems involved, respectively) an initial structure of the chromophores (r,τ,ξ,ϕ) may be created and the ligand system may be wrapped around the metal centers with molecular graphics. The resulting initial structure of the dimer can then be refined with MM, leading to a new set of the geometric parameters r,τ,ξ,ϕ used for the simulation of the EPR spectrum. This process (MM-EPR) may be repeated for various conformers obtained from building molecular geometries with a fixed orientation of the two metal centers.

The MM-EPR scheme has been tested for a number of dinuclear copper(II) complexes and, where experimental (X-ray) structures were available, the agreement between these and computed struc-

tures is satisfactory.[29,30] It is important to note here again that some differences between crystal and solution structures are not unexpected for two reasons: (i) The computed structures are MM refinements, and therefore small errors due to deficiencies in the force field and the neglect of environmental effects may not be prevented. (ii) Copper(II) is labile. Thus, the crystal and solution structures may not be identical (see Introduction), viz. ligands may be exchanged, especially the very labile axial ones. A change from coordinated anions in the crystal lattice to solvent molecules in solution may lead to a preference for a different coordination geometry. The structure determined by the MM-EPR method reflects the situation in solution and corresponds to the global energy minimum in the solvent used for the EPR experiment.

A relevant case of a dinuclear copper(II) species will be discussed below. An intriguing mononuclear copper(II) system related to this problem is the $[Cu(ahaz)_2]^{2+}$ system (ahaz = 3-aminohexahydroazepine, see Fig. 5).[31] With optically pure (S)-ahaz the purple square pyramidal $[Cu((S)\text{-}ahaz)_2X]^{n+}$ (X = ClO_4^- in the crystal, X = OH_2 in aqueous solution) obtains (shown in Fig. 5 is the MM refined structure).[31] With racemic (R)-ahaz/(S)-ahaz the *orange* square planar $[Cu((R)\text{-}ahaz)((S)\text{-}ahaz)]^{2+}$ complex[31,32] precipitates out of a *purple* solution, indicating the thermodynamic preference but higher solubility of the square pyramidal structure ($[Cu((S)\text{-}ahaz)_2(X)]^{2+}$ or $[Cu((R)\text{-}ahaz)_2(X)]^{2+}$).

The frozen solution EPR spectrum of the copper(II) complex of the quadridentate ligand mnpama (ama = gly: 5-methyl-5-nitro-3,7-diazanonanedioate, R^1 = R^2 = H, see Fig. 6) indicated that the major species in solution is a dicopper(II) complex in equilib-

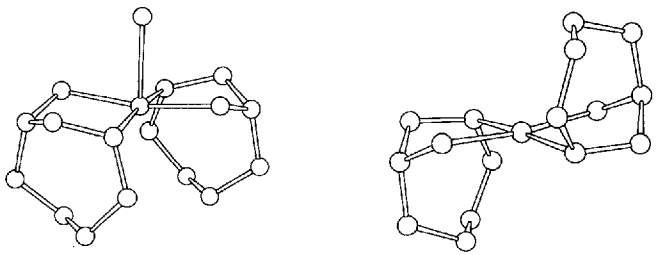

FIGURE 5 Calculated structures of $[Cu((S)\text{-}ahaz)_2(OH_2)]^{2+}$ and $[Cu((R)\text{-}ahaz)((S)\text{-}ahaz)]^{2+}$

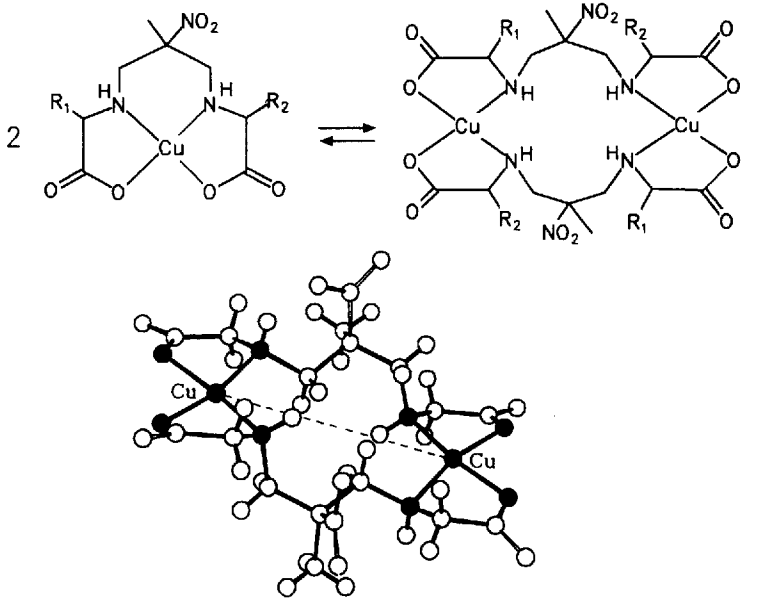

FIGURE 6 The equilibrium involving monomeric and dimeric $\{[Cu(mnpgly)]\}_n$ (n = 1, 2), and the calculated structure of the dinuclear compound.

rium with a monomer. Again, the only species isolated was not the more abundant but the less soluble mononuclear complex, as shown by a crystal structure.[33] No X-ray data of a dinuclear copper(II) species with mnpama (ama = gly, ala, val, leu, phe, etc.) are available; all crystallise as monomers[33,34] (only a few lead to dinuclear complexes in solution; see ahead). The calculated geometry (MM) of the monomer is in good agreement with the crystal structure,[33] and further support for the MM-EPR structure of the dimer shown in Fig. 6 comes from thermodynamic observations. The strain energy of the dimer is less than half of that of the monomer, indicating that it is more abundant in solution (environmental effects neglected). This is true only for ama = gly and the mixed gly/ala species ($R^1 = R^2 = H$ and $R^1 = H, R^2 = CH_3$) and for the similar ligands where the pendent nitro group is reduced to a pendent amine. For all others the dinuclear form is less stable and indeed it is not observed experimentally.

MM-AOM

AOM calculations allow the computation of d-electron energy levels of a transition metal complex, based on the geometry of the chromophore and bonding parameters (e_σ and e_π) for all ligand atoms.[35,36] The model is usually used for the *interpretation* of electronic properties (UV-vis-NIR, EPR spectra, magnetic moments). For the *prediction* of spectroscopic data based on an established structure (experimental or MM), a *known and therefore transferable* set of electronic parameters must be used. This property of the parameterization is not a priori given in the AOM model and therefore of some concern.[31,37,38] The successful test of the MM-AOM approach with constant parameterizations for Cr(III), Co(III), and Ni(II) hexaamines,[37] Cu(II) tetraamines[31] and *low spin* Fe(III) hexaamines[38] does not imply that the bonding parameters are strictly transferable; it just means that, for the systems considered so far (as large as possible structural variations were included in the series of compounds investigated), the errors induced via a putative transferability are tolerable.

We have used different bonding parameters for various degrees of alkyl substitution on the amines: due to inductive effects one would predict that the e_σ parameters increase in the order $NH_3 < NH_2R < NHR_2 < NR_3$, an effect which directly emerged from our studies.[37] The *e*-values were adjusted for structural effects based on the MM or crystal structures: for the reduction of the *e*-values with bond elongation we used a $1/r^6$ function (r is the metal–ligand distance), and reduced σ-bonding due to bent bonds was approximated with a $\cos^2\alpha$ function (a π-bonding correction was not included).[31] Constant parameters for electron repulsion were used, although a small dependence on bond length (bond strength) is expected. The AOM calculations were performed with a modified version[39] of CAMMAG.[40]

Some selected results (strongest and weakest bond each to demonstrate the range of observed (and calculated) spectroscopic parameters) are given in Table III. The error limits for electronic transitions of the order of 800 cm^{-1} (range ca. 2000–5000 cm^{-1}, depending on the metal ion), for *g*-values of ca. 2% and for *A*-values of the order of 10×10^{-4} cm^{-1} (range ca. 170–210 10^{-4} cm^{-1}) are appreciable but satisfactory in view of the simplifications

TABLE III

Selected results of MM-AOM calculations in comparision with experimental results (Refs. 31, 37 and 38).

Compound	Parameter[a]	Calculated Value[b]	Experimental Value[b]
$[Cr(NH_3)_6]^{3+}$	$^4A_{2g} \rightarrow {}^4T_{2g}$ $^4A_{2g} \rightarrow {}^4T_{1g}$	21450 28800	21100 28900
$[Cr(trans\text{-diammac})]^{3+}$		23730 31500	23430 30120
$[Co(tn_3)]^{3+}$	$^1A_{1g} \rightarrow {}^1T_{1g}$ $^1A_{1g} \rightarrow {}^1T_{2g}$	20480 29000	20600 28500
$[Co(trans\text{-diammac})]^{3+}$		22280 30720	22370 30490
$[Ni(NH_3)_6]^{2+}$	$^3A_{2g} \rightarrow {}^3T_{2g}$ $^3A_{2g} \rightarrow {}^3T(F)_{1g}$ $^3A_{2g} \rightarrow {}^3T(P)_{1g}$	10730 17150 27770	10750 17500 28200
$[Ni(trans\text{-diammac})]^{2+}$		13500 19500 32200	13160 20500 31970
$[Cu((R,S)\text{-ahaz})_2]^{2+}$	$g_{\parallel}$ $A_{\parallel}$	2.16 205	2.14 207
$[Cu(mnp[15]N_4)]^{2+}$		2.19 194	2.21 193
$[Fe(en)_3]^{3+}$	g_1 g_2 g_3	1.35 2.55 2.55	– 2.68 2.68

[a]O_h symmetry.

[b]Electronic transitions in cm^{-1}, A-values in 10^{-4} cm^{-1}.

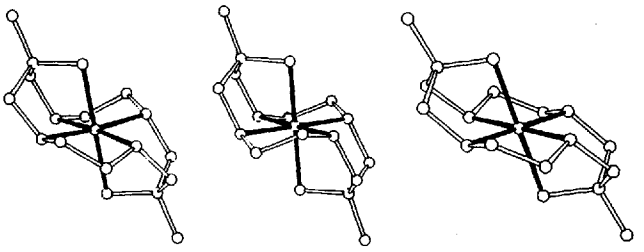

FIGURE 7 Calculated structures of the three conformers of [Fe(*trans*-diammac)]$^{3+}$.

TABLE IV

Observed and calculated structural and spectroscopic parameters of [Fe(*trans*-diammac)]$^{3+}$ (Ref. 38).

Isomer	Θ	g_1	g_2	g_3	Strain Energy [kJ/mol]
structure A	11.0	1.42	2.61	2.81	
structure B	9.5	1.51	2.61	2.78	
structure C	11.3	1.62	2.48	2.84	
solution		1.63	2.46	2.84	
δδ	9.2	1.45	2.54	2.95	90.7
λδ	3.5	0.95	1.96	3.29	91.5
δλ	15.7	1.89	2.05	2.46	112.2

adopted. Also, semi-empirical and ab initio calculations of similar systems have led to predictions with inferior quality.[41-43]

To demonstrate the utility of the method I will now discuss one system, [Fe(*trans*-diammac)]$^{3+}$ in detail (see Fig. 7 and Table IV; *trans*-diammac = *trans*-6,13-dimethyl-1,4,8,11-tetraazaundecane-6,13-diamine). The three reported experimental structures of the *low spin* iron(III) complex all have disordered five-membered chelate rings, making an assignment of the conformation practically impossible.[38] From the MM calculations alone the δλ conformer may be excluded due to a ca. 20 kJ/mole higher strain energy. The two other conformers are predicted to have similar abundance. However, the experimentally observed *g*-values are in agreement with the computed parameters of only the δδ/λλ conformer; the λδ conformer is far outside the generally observed error limit,

suggesting that the observed EPR spectra are due to the δδ/λλ conformer.

CONCLUSION

Two of the most important problems of MM are that environmental effects (crystal lattice or solvent sheath) are generally neglected and that the attribution of the global energy minimum is not generally possible. While the first problem may theoretically be solved at the expense of CPU time, the latter problem does not have an exact solution. The general approach to simulate experimental data based on computed (MM) structures is an appealing way to approximately solve both problems. However, one should be careful not to become overconfident about the results of this technique. The MM refinement discussed in the various examples still does not include environmental effects, while the experiments used in all cases were performed in (aqueous) solution. Nevertheless, it appears that any observed discrepancy between the simulated experimental property based on the MM refinement and the experimentally determined value is the result of inconsistencies in the algorithms and parameterization schemes used (MM and simulation of experimental properties) rather than the result of neglected environmental effects in the strain energy minimization process.

The main challenge is to find theoretical models with appropriate algorithms and general parameterization schemes which are simple enough to allow a quick and meaningful calculation of experimental properties based on experimental or calculated molecular structures.

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