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Metal ion selectivity and molecular modeling

Peter Comba *

Anorganisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

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Contents

Abstract

The evaluation of ligand molecules that are able to coordinate selectively specific metal ions is a difficult task. Possible applications range from metal refinement and detoxification of industrial waste to medical applications and the desire to understand biological processes. Molecular mechanics modeling was used to predict highly preorganized ligand systems and the molecular mechanics design, followed by the synthesis of size selective macrocyclic donors was used extensively in this area. So far, only few truly successful studies have emerged, and some of these are reviewed. The limitations of the models used are highlighted, the reasons for expected pitfalls are discussed and possible models to solve some of the remaining problems are analyzed.

Keywords: Metal ion selectivity; Molecular mechanics; Force fields; Complex stability; QSAR

* Tel.: + 49-6221-548453; fax: + 49-6221-546617.
E-mail address: comba@akcomba.oci.uni-heidelberg.de (P. Comba)

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1. Introduction

Ligands that are able to selectively build strong coordination compounds with specific metal ions are of importance in many areas [1–7]. Metal ion selective ligands are used in medicine, for the treatment of metal intoxication [8–12], the complexation of paramagnetic metal ions used in magnetic resonance imaging (MRI) [13–17] and for complexation of radio isotopes used for imaging and therapy of tumors [18–22]; in environmental sciences, for waste water treatment and for the quantitative analysis of soil, water and air [23,24]; in industry, for separation and recycling in hydrometallurgic processes [25,26]; in fundamental research, to understand the selectivity in metal ion transport through the cell wall [3,27], in binding to siderophores, ionophores [3,28] and proteins [8,29], and to understand the effects of ligand systems on reduction potentials of transition metal coordination compounds, that is, the stabilization of uncommon oxidation states of transition metal ions by coordination to specific ligand systems. Thus, there have been and still are enormous efforts for the rational design of metal ion selective ligands. All approaches used in this area are based on a thorough understanding of complex stability (or complex stability differences), as in Eqs. (1)–(3):

$$M_{aq}^{n+} + L_{aq} \overset{K}{\rightleftharpoons} ML_{aq}^{n+} \tag{1}$$

$$K = e - \frac{\Delta G_c^\circ}{RT} \tag{2}$$

$$\Delta G_c^\circ = \Delta H_c^\circ - T\Delta S_c^\circ \tag{3}$$

The complexation reaction involves desolvation of the metal ion and of the ligands, the complexation process and solvation of the complex. Electronic effects (metal ion–donor atom bonding), steric effects (e.g. preorganization of the ligand, size-fitting), entropic terms (e.g. chelate and macrocycle effects), solvent dependencies (i.e. solvation and ion-pairing) are the basis of complex stability. These are requirements that, so far, have not been met altogether in a general approach for the accurate and, in terms of computational expense, acceptably fast calculation of metal ion selectivities. There are a number of concepts that are used in the interpretation and prediction of complex stabilities and in related areas (e.g. the prediction of reduction potentials [30–38], the correlation of reduction potentials with ligand field strengths [39–41] and NMR chemical shifts [42]). Some of these approaches are purely qualitative, others allow (semi-)quantitative predictions but all are, for the reasons given above, limited in their applicability. Electronic factors (bond strengths) are often interpreted on the basis of Pearson's HSAB principle [43], the Irving–Williams series [44–47] and general ligand field effects [32,39–41,46,47]. The approaches to quantity steric effects range from the concepts of cone angles [48–50] and seat–ligand–fitting [51–53], the VSEPR [54,55] and ligand–ligand repulsion models [56–58] to the computation of ligand bonding cavities [1,59–61] and force field calculations in general [62]. Molecular mechanics has often been used in the area of the prediction of metal ion discrimination [1,6,7,59–72]. However, in many of these examples the straight relation to the computation of

metal ion selectivity is not obvious and limitations and pitfalls are not clearly discussed. In this report I will mainly concentrate on force field based methods, stress the problems, critically discuss a few (partly) successful examples and try to indicate possible approaches that might in future lead to methods that allow the prediction of metal ion discrimination.

2. Steric effects and beyond

2.1. Preorganization

The coordination of ligand molecules to a metal ion induces strain by the metal center to the ligand molecule and strain by the ligand to the metal center [41]. The loss of steric energy is compensated by the bonding energy that results from metal ion–donor atom bond formation (Eq. (4)):

$$\Delta G^{\circ}_{c} = (\Delta H^{\circ}_{ML} + \Delta U_{strain}) - T\Delta S_{c} \quad (4)$$

In a fully preorganized ligand the structure of the metal-free ligand is identical to that of the coordinated ligand [73,74], else ΔU_{strain} (the difference of strain energy between the metal-free and the coordinated ligand) is positive (note that it is possible to include steric strain that involves the metal ion–donor atom stretching mode; this does, however, not fully include the metal ion/donor atom pair dependent electronic part of ΔH°_{ML}). It follows that preorganization refers to a specific metal ion/ligand pair, and it involves the size and shape of the bonding cavity of the ligand (that is, the ligand preferences) and the preferences of the metal ion. Size- and shape-selective ligands need to be highly preorganized and the energy cost for their structural reorganization needs to be large, else they do not discriminate enough. That is, the ligand needs to be highly preorganized and rigid. The main flexibility of ligand molecules is torsional freedom that involves single bonds. That is, flexible ligands may easily adapt to metal ions of variable size. This may be restricted by multiple bonds, small ring systems and sterically demanding substituents [41]. This is the general basis of molecular mechanics with the aim of a rational design of metal ion selective ligand systems. Note again, that, usually, this does not account for ΔH°_{ML}, and it does not fully account for $-T\Delta S_{c}$ in Eq. (4).

2.2. Molecular mechanics—general aspects and limitations

The general assumption of molecular mechanics is that the positions of all atoms of a molecule are determined by forces between each atom and all the others. A set of potential energy functions describes the bonds, angles, torsional angles, van der Waals and electrostatic interactions and some other terms. Structures are optimized by minimizing the resulting total strain energy. Thus, the results of a molecular mechanics calculation are an optimized structure and the corresponding minimized strain energy (depending on the minimization

algorithm used, vibrational frequencies may also be obtained). These general principles and the inherent limitations, specifically in the area of coordination compounds, have been discussed in an increasing number of books and review articles [62,75–83]. Important factors are that (i) molecular mechanics is a fully interpolative method, that is, the results depend on the data base to which the force field (functional form and parameterization) has been fitted; (ii) for applications that involve the computation of thermodynamic parameters (complex stabilities) force fields that are fitted to experimental structures—and this usually is the case in the area of transition metal ion compounds—are not appropriate [62] (reasons for the fact that, nevertheless, fortunately the steepness of the potential energy surfaces generally is rather accurate have been discussed in detail [41,62,84]); (iii) strain energies are relative quantities; thus, only strain energy differences between isomers may be used for thorough interpretations (note, that this may be a serious problem in the area of metal ion selectivities); (iv) environmental effects (solvation and ion pairing) and entropy terms are often neglected in molecular mechanics studies; note, that there are possibilities to optimize solvated and ion-paired compounds and to compute entropies [62,84–92], and the correlation of strain energies with (computed) solvation energies and entropies has been discussed [32,33].

In addition to these general approximations and limitations there are two points which are especially important for applications in the area of metal ion recognition: (i) metal ion selectivity is based on the difference of the complexation free energies $\Delta(\Delta G_c^\circ)$ between two or more metal ions and a common ligand (Eq. (4)), where the difference between the strain energies $\Delta(U_{strain})$ (degree of preorganization) is only one term. That is, electronic effects (metal ion–donor atom bonding) are of importance, and these are generally not easy to quantify; (ii) the result of an optimization of a structure by strain energy minimization depends on the starting structure; while there are methods to scan the conformational space and while some force fields allow flexibility in terms of the coordination geometry (points-on-a-sphere models in particular), coordination modes and coordination numbers must usually be defined in the starting model. This is a serious restriction and a relevant example is EDTA which may bind as a 5- or 6-coordinating ligand, and 6-, 7- and 8-coordinate $[M(EDTA)(OH_2)_n]^{m+}$ complexes have been observed) [62,93].

2.3. Force fields: the problem of transferability

The enthalpy ΔH_c^{ML} of complex formation may be correlated with the corresponding strain energy terms (Eqs. (5) and (6)):

$$M + nL \rightleftharpoons ML_n \tag{5}$$

$$\Delta H_c^{ML} \approx U_{strain}^{total} = U_{strain}^{ML_n} - U_{strain}^{M_{aq}} - nU_{strain}^{L_{aq}} \tag{6}$$

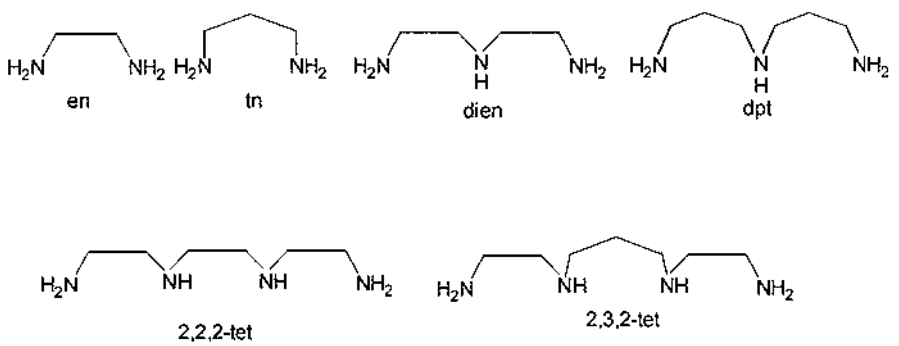
This approach has been used successfully to verify the influence of the chelate ring size for a series of nickel(II) amine complexes (Table 1). The good agreement between the observed and computed stability sequences indicates that, in this case, the differences as a function of the chelate ring size are dominated by steric strain [63].

It emerges that Eq. (6) may be used to compute the steric energy contribution of a complexation reaction. Note, that all data in Table 1 are on nickel(II) amines with the same number of donor groups in each pair. Therefore, the bonding energy term (see Eq. (4)) is constant (see also below). However, this approach requires transferability of the force field between metal-free and coordinated ligands. Obviously, this approximation may not be valuable in general: there is some electron transfer between the donor and the metal center [62,94]. The recent development of a new force field that distinguishes between metal-free and coordi-

Table 1
Experimentally determined and calculated stability constants of high spin nickel(II) amines with five- and six-membered chelates [63]

Complex	U (kJ mol^{-1}) MM	$-\Delta U$ (kJ mol^{-1})[a] MM	ΔH (kJ mol^{-1}) obs	$-\Delta(\Delta H)$ (kJ mol^{-1}) obs
Ni(en)	0.27		−2.15	
Ni(tn)	0.73	0.37	−1.86	0.29
$Ni(en)_2$	0.80		−4.37	
$Ni(tn)_2$	1.71	0.73	−3.59	0.79
$Ni(en)_3$	1.09		−6.69	
$Ni(tn)_3$	3.14	1.78	−5.09	1.60
Ni(dien)	1.45		−2.84	
Ni(dpt)	1.98	0.35	−2.53	0.31
$Ni(dien)_2$	2.84		−6.05	
$Ni(dpt)_2$	5.10	1.91	−4.21	1.84
Ni(2,2,2-tet)	2.26		−3.35	
Ni(2,3,2-tet)	1.75	−0.60	−4.28	−0.93

[a] Corrected for strain energy differences of the free ligands



nated ligands takes account of this problem [95]. The observed effects are rather small, and this may explain why studies on metal ion selectivity with variants of Eq. (6) that assumed full transferability of the parameters did not lead to undue inaccuracies [62,68,70,71,94,95].

2.4. Preorganization: metal ion versus ligand selectivity

Molecular mechanics is a valuable tool to quantify the preorganization of a ligand with respect to a specific metal complex and therefore, to design highly preorganized ligands (see examples given below). This is because, based on a high quality force field, molecular mechanics allows to design a ligand with a given donor set that has an optimum fit (preferred coordination geometry). However, maximum *stability* is not necessarily equal to optimized *discrimination*. Selectivity means that the stability for one metal ion needs to be optimized while the stability for all the others is minimized. The problem with respect to the metal–donor bonding energy terms has been discussed above. In terms of the steric energy the problem to solve is that the design of a metal ion selective ligand must involve a high degree of preorganization for a specific metal ion and also a high degree of 'disorganization' or 'mismatch' for other metal ions. The latter is not an easy task since this reverts the ligand design from a one- to a multidimensional problem and, indeed, this aspect has not been addressed in detail so far.

Quite often, therefore, reports on the molecular mechanics design of metal ion selective ligands involve the strain energy optimized structures of a series of ligand derivatives and the corresponding metal complexes—sometimes involving a single metal ion. Clearly, this type of study is not directly related to the design of metal ion selective ligands but rather to the design of 'ligand selectivity by a metal ion or by a few metal ions'. In practice this is a much less interesting problem to solve and it leads to much less revealing and less applicable results.

3. Applications

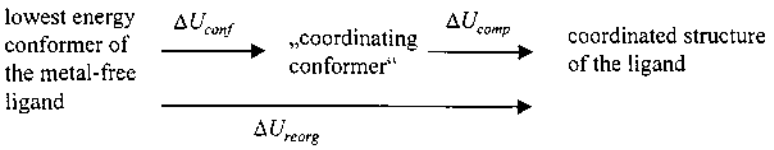
3.1. Quantitative assessment of the degree of ligand preorganization

The degree of preorganization of a metal-free ligand must be defined with respect to the structure of the ligand in the corresponding coordination compound with a specific metal ion. Optimization of the degree of preorganization, on the basis of a constant donor set and topology of a ligand molecule, may help to optimize complex stability. Oligothiamacrocylic ligands are especially valuable examples here since these are known to prefer, in contrast to the corresponding oxa- and aza-macrocycles, exodentate conformations [96–101]. The degree of preorganization (or complementarity) of the metal-free ligand involves the size and shape of the ligand cavity. The amount of reorganization that is necessary for the coordination of the ligand molecule to a specific metal ion must involve the structure and/or strain energy of the metal-free ligand and the ligand structure and/or ligand-based

strain energy when it is coordinated to the metal ion. Thus, these structural and strain energy differences are useful for the comparison with experimental (thermodynamic) parameters. The general approach for obtaining this information includes the experimentally determined or computed structures of the metal-free ligand and of the metal complex, and the comparison of the structures and/or strain energies of the two geometries of the ligand molecules, that is, for the coordinated ligand the strain energy has to be computed after removal of the metal ion. Note that this general approach may allow to obtain a meaningful idea of the degree of preorganization of a particular ligand with a series of metal ions (metal ion selectivity) or of a series of ligands with a specific metal ion (optimization of a ligand system or 'ligand selectivity', see above).

The structural reorganization of a ligand was considered to be a two step process that involves a conformational ligand reorganization term ΔU_{conf} from the most stable conformation of the metal-free ligand to that of the coordinated ligand ('coordinating conformer', reorganization prior to the complexation reaction), and a structural reorganization term ΔU_{comp} that occurs during the complexation reaction and is a measure of the complementarity of the ligand molecule (see Chart 1, Eq. (7)) [68].

(Chart 1)

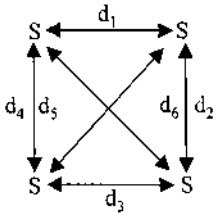


$$\Delta U_{\mathrm{reorg}} = \Delta U_{\mathrm{conf}} + \Delta U_{\mathrm{comp}} \tag{7}$$

Note that the mechanism of complexation by a macrocyclic ligand is, depending on the type of ligand and metal ion involved, a step-wise process that does not necessarily involve the 'coordinating conformer' [102,103]. Thus, the splitting of the ligand structural reorganization into two terms that occur before and during the coordination is arbitrary and, in terms of the complexation mechanism, not necessarily reasonable. However, it may allow to separate specific factors of importance for the ligand design, such as the rigidity (related to the conformational reorganization) and the cavity size and shape of a ligand (related to the complementarity). Binding sites of alkylated bidentate ether ligands have been correlated with this method to the corresponding stability constants [68].

A strain energy-based and a structural reorganization parameter were used to assess the preorganization of structurally reinforced tetrathiamacrocyclic ligands [69]. Both parameters are based on the experimentally determined and/or computed structures of the metal-free and the coordinated ligand molecules. The strain energy ratio $E_{\mathrm{L}}/E_{\mathrm{C}}$ ($E_{\mathrm{L}} = U_{\mathrm{strain}}$ (metal-free ligand); $E_{\mathrm{C}} = U_{\mathrm{strain}}$ (coordinated ligand)) was used as a parameter that is related to the thermodynamics of the reorganization process; the sum of the absolute values of the differences of the intramolecular donor–donor distances $\Sigma_{n=1}^{6}|\Delta d_n|$ (see Chart 2) was used as a structural parameter related to the ligand reorganization.

(Chart 2)



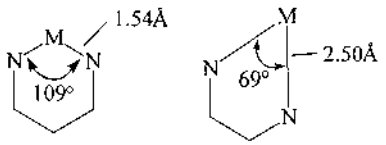
$$\sum_{n=1}^{6}|\Delta d_n|$$

A fully preorganized ligand has $E_L/E_C = 1$ and $\Sigma_{n=1}^{6}|\Delta d_n| = 0$, generally $E_L/E_C < 1$ and $\Sigma_{n=1}^{6}|\Delta d_n| > 0$. These are fully empirical correlations and there is no justification for using the strain energy ratio E_L/E_C instead of the strain energy difference $E_C - E_L$ for the assessment of the preorganization (other terms, such as $(E_C - E_L)/(E_C + E_L)$ were used with similar results [69].

3.2. Chelate ring size effects

For both amine [7,63] and (ether) oxygen donors [7,104] there is a selectivity of five-membered chelate rings for relatively large metal ions while six-membered chelate rings prefer relatively small metal ions. A simple geometric model is often used to interpret these observations [6,7,63,65,105]: for a six-membered chelate ring three appropriate corners of a cyclohexane molecule (chair conformation) are replaced by a metal ion M and two amine nitrogen (or ether oxygen) donors N, leading to a putative metal-1,3-diaminopropane ($[M(tn)]^{n+}$) chelate with M–N distances of 1.54 Å and an N–M–N angle of 109.5°. In a similar model a metal–1,2-diaminoethan ($[M(en)]^{n+}$) chelate leads to M–N distances of 2.50 Å and an N–M–N angle of 69° (Chart 3).

(Chart 3)



This crude model neglects the variation in plasticity (or rigidity) and the variable preferences of metal ions. The metal–donor distances, the donor–metal–donor angles, and the angles around the donor atoms are coupled, that is, the optimum structure largely depends on the relative steepness of the three potentials involved (metal donor stretching and the two angle bending terms; potentials involving the carbohydrate backbone usually are much stiffer) [41,62,79,84]. The fact that, with a given metal ion, metal–amine, metal–1,2-diaminoethane and metal–1,3-diaminopropane compounds often have similar metal–nitrogen bond distances and angles involving the metal center and the donor atoms [41,76,84,106,107] indicates that the directionality exerted by the metal center and the donor atoms are of some importance (the directionality of the metal center–donor bonds is comparatively weak, however (plasticity of transition metal ions), and this was discussed in some detail [108]). Also, the angular dependence involving the donor groups was discussed as one of the primary factors in the determination of complex stability of crown ether ligands [66]. A well-balanced force field must take all these factors into

account (note that a force field that is only based on experimental structures, i.e. a force field that was not validated with thermodynamic data, might not fulfill these requirements, see above).

3.3. Bonding cavity shapes and sizes

The calculation of the hole size of macrocyclic ligands is by far the widest area of application of molecular mechanics toward the design of metal ion selective ligands. A ligand with a hole that entirely fits a specific metal ion, that is, a highly preorganized ligand, leads to maximum stability. Rigidity of the macrocycle prevents the ligand from adapting to a variety of metal centers and therefore enhances the selectivity. From the fact that metal ions do not merely need to fit into the hole, but that they need to be fixed (bound) to the cavity, it emerges that the ligand cavity must have a specific size and shape, that is, the number and type of donors, their angular orientation around and the distance to the metal center and the directionality of the donor lone pairs with respect to the metal–donor vectors are of importance [41,72,84]. The rigidity of the ligand also refers to the size and the shape of the cavity.

A number of primarily molecular mechanics based methods for the computation of ligand cavity sizes have been reported (note that cavity shapes and sizes are not necessarily restricted to macrocyclic ligands). These have been discussed in detail and controversially and corresponding results have been reviewed extensively [1,7,59–62,75,109–112]. Molecular mechanics based approaches generally compute the ligand-based strain energy as a function of the metal–donor distance. Based on the often used harmonic potential (Eq. (8)) there are three main methods to scan the potential energy surface as a function of the M–L distance:

$$U_{\text{strain}}^{\text{ML}} = 1/2k^{\text{ML}}(r^{\text{ML}} - r^{\circ}) \tag{8}$$

- variation of r°;
- restraints, i.e. fixing of r^{ML} by (exceedingly) large force constants;
- constraints, i.e. fixing of r^{ML} mathematically (this is only possible when minimization techniques are used that include second derivatives).

Constraining bond distances (or other internal parameters) with Lagrange multipliers probably is the most elegant method since it is mathematically precise and does not lead to artefacts. Also, it may be used to compute ligand cavities without metal ion dependent energy terms. This is a requirement for the computation of metal ion selectivities [62,72,75].

Ligand systems used for the selective binding of metal ions are only rarely symmetrical. The asymmetry may be based on the ligand backbone and/or the donor set. It is astonishing that only recently it was pointed out that erroneous results are expected when all metal–donor distances are varied uniformly for asymmetrical ligands [62,113]. From the methods that have been proposed to shrink and blow-up cavities asymmetrically, the most elegant is to use Lagrange multipliers on the sum of a selected number of bonds (that is on all metal–donor distances; sum constraints) [72,114]. This allows to scan a bonding cavity under the condition

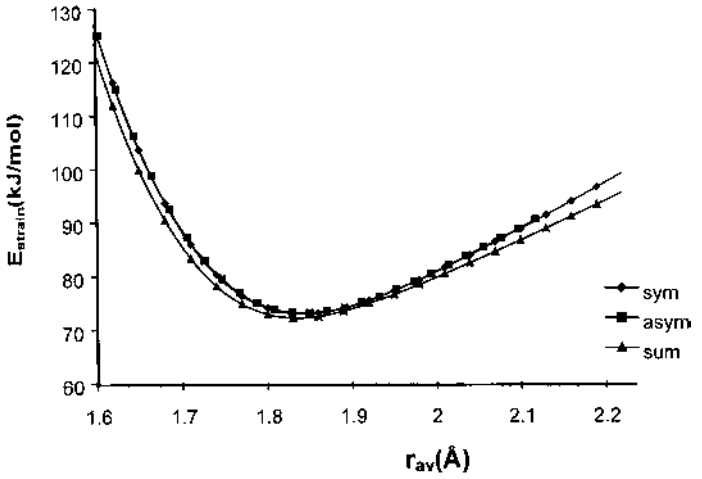
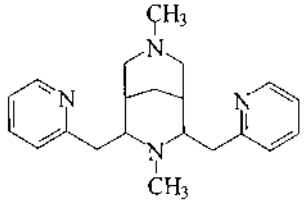
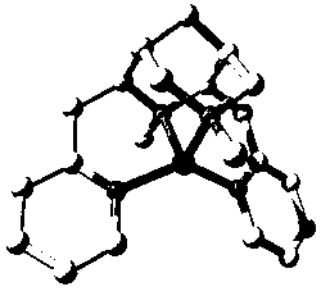


Fig. 1. Strain energy E_{strain} as a function of the average M–N bond distance r_{av} for $[M(bispidine)]^{n+}$ (see Chart 4 for ligand structure). sym, symmetrical variation of the hole size; asym, asymmetrical variation of the hole size [115]; sum, variation with sum constraints [71].

that each bond that is included in the constraint may react individually to the stress imposed by enforcing a certain cavity size. Similar methods may be used to scan the shape of a cavity by constraining sets of valence or torsional angles but this has not been done so far. An example of the computation of the cavity size and shape is given in Fig. 1 (see Chart 4 for the structure of the corresponding bispidine type ligand). The important result is that the optimum cavity size (1.78, 1.81, 1.84 Å) and the relative energy cost upon shrinking and blowing-up the ligand (steepness of the total energy curve) depend to some extend on the approach used (the force field was the same for the computation of the three curves) [72].

(Chart 4)





The lowest energy curve in Fig. 1 fulfills all the requirements for the computation of the shape and size of a ligand cavity: it is metal-ion independent (all metal dependent terms are removed: a points-on-a-sphere model is used, i.e. angle bending potentials around the metal center are replaced by 1,3-nonbonded interactions and metal–donor potentials are set to zero) and sum-constraints are used for metal–donor bonds, i.e. elongation and compression of all four bonds are decoupled. Hence, the plotted strain energy of this curve is the strain induced by a metal ion to the ligand without any metal ion present. The important questions are what the significance of such a curve is and how its accuracy may be checked. The naive answer to the first question is that the bispidine ligand (Chart 4) prefers very small metal ions (M–L $\sim$1.8 Å, see Fig. 1) and that elongation to ca. 2.0 Å leads to a destabilization of over 10 kJ mol^{-1}. However, there is no reason to assume that real metal ions would not capture another ligand present in solution (solvent, anions) to produce five- or six-coordinate [M(bispidine)X_n]$^{m+}$ species ($n = 1, 2$) with different cavity shapes and sizes. Also, the ratio of ideal bond distances and force constants involving the bonds to the amine and to the pyridine donors might differ from metal ion to metal ion. This indicates that, dependent on the problem to solve, the fictive metal ion independent cavity size and shape may or may not be a relevant parameter. The simple answer to the second question is: there is no way to check the correctness of the curve. Experimental proof for the metal ion independent curve (measurement of stability constants) will not be possible (see above) and the computation of strain energies of individual metal complexes does involve (individual) metal dependent terms. That is, data points that are based on computed structure and strain energy pairs are not expected to coincide with he computed metal-independent curve. Structures (and thermodynamic properties) of transition metal coordination compounds are the result of a compromise between metal ion and ligand preferences. Metal ion independent cavity size (and shape) computations may be used to quantify the ligand preferences. The problem with the interpretation of these curves arises because it is not an easy task to compute the metal ion preferences separately and to predict the metal ion dependent balance between ligand and metal ion dictation.

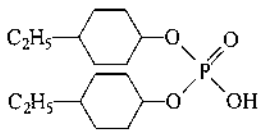
3.4. Quantitative structure stability relationships

Molecular and materials properties are related to structures [62,76,79,84]. Obvious examples include the destabilization and enhanced reactivity due to steric strain, the dependence of the ligand field strength from metal–donor distances and angular distortions, Karplus relations in NMR spectroscopy, stabilization by hydrogen bonding, etc. Hence, there must be algorithms that relate (calculated or observed) structures and strain energies (that is, the results of force field calculations) with thermodynamic properties, reactivities, electronic and spectroscopic properties. The mathematical models used are generally based on pattern recognition methods and the resulting models may be used for interpolations. That is, the quality and applicability of these models depends on the quality and variability of the 'training set' of observables.

A number of quantitative structure–property relationships (QSPR) have been used for the design of new compounds, for the interpretation of their properties and for the determination of structures [76,79,84,90,115–117]. These include linear and non-linear correlations of (computed) structural parameters and strain energies with complex stabilities [6,66,70,71,118], reduction potentials [32,33,39,119], electron transfer rates [32,120,121] and ligand field properties [41,107,122–124], and the computation of IR, NMR and EPR spectra, based on structural information [84,117,125–128]. Quantitative structure–activity relationships (QSAR), which are used in drug design for almost 30 years [129], use a mathematical model to relate numerical properties of the molecular structure to the activity of the substance. The electron topological approach (ET) is an extension of simple QSAR methods which, as a third dimension, includes information on electronic features [130].

Linear regressions have been used for the correlation of complex stabilities with the strain energies of transition metal coordination compounds [6,66,70,71,118]. For lanthanoid(III) compounds with bis-alkylhydrogenphosphates (Chart 5) the strain energy of the complexation reaction ΔU_M is (Eqs. (9) and (10)):

(Chart 5)



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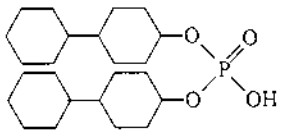

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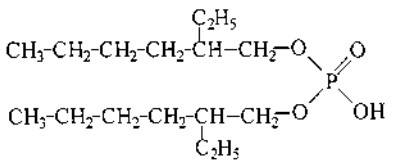

HR = D2EHPA

$$\underset{\Delta U_M}{M(OH_2)_9^{3+}} + \underset{6U_{HR}}{6HR} \rightarrow \underset{U_{Mcom}}{M\{(HR)(R)\}_3(OH_2)_3} + \underset{3U_H}{3H^+} + \underset{6U_{aq}}{6H_2O} \quad (9)$$

$$\Delta U_M = U_{Mcom} + 3U_H + 6U_{aq} - U_M - 6U_{HR} \quad (10)$$

With M = La(III) as a reference the relative strain of the complexation reaction is (Eq. (11)):

$$\Delta U_M - \Delta U_{La} = (U_{Mcom} - U_{Lacom}) - (U_M - U_{La}) \quad (11)$$

The correlation of the relative strain energies of the complexation reaction with the relative extraction constants leads to a linear plot (Eqs. (12) and (13); Fig. 2; α is the apparent QSPR constant with an expected value of 1.08) [70].

$$\Delta G_M = -RT \ln K_{ex,M} \quad (12)$$

$$\Delta U_M - \Delta U_{La} = \alpha \log (K_{ex,M}/K_{ex,La}) \quad (13)$$

The small deviation of α from the expected value (1.26 vs. 1.08) is probably due to the neglect of entropy, ion-pairing and solvation (see above). The good linearity suggests that the neglected terms are constant or linearly dependent on the strain energy. A similar observation was made when reduction potentials of hexaaminecobalt(III/II) and tetraaminecopper(II/I) couples were correlated with strain energy differences between the oxidized and the reduced forms [32,33].

What is the value of a correlation such as that presented in Fig. 2? All three ligands (Chart 5) fit to the same curve with a slope of 1.26, and other derivatives with similar donor sets that lead to complexes with the same stoichiometry (Eq. (9)) will probably also fit to the curve. Thus, a plot such as that of Fig. 2 is a valuable test for the type of structure and extraction mechanism of a new ligand system. Does it also help to design new ligands with increased selectivities? The linear correlation between the relative complexation strain energy and the relative extractabilities indicates that, as expected, increasing bulk of the substituents of the organophosphato ligands results in increasing selectivity. With the force field used

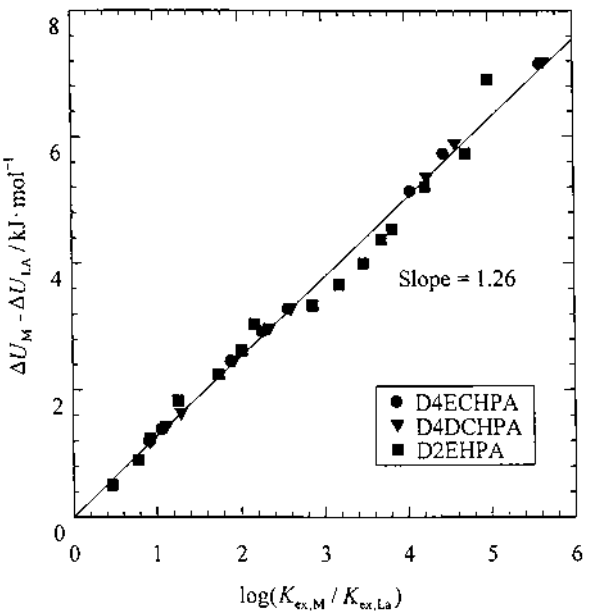

Fig. 2. QSPR plot of $\Delta U_M - \Delta U_{La}$ vs. $\log(K_{ex,M}/K_{ex,La})$ (for ligand abbreviation see Chart 5).

[70,95], this may be predicted quantitatively. However, there is a limit, where excessive strain might lead to a change in coordination number, and this cannot be predicted with harmonic bonding potentials as they were used in the investigation discussed here.

4. Conclusions and possible extensions

The neglect of entropic terms, of environmental effects (solvation, ion pairing), of specific metal–donor bonding terms (electronic effects) and of anharmonicity in the metal–donor stretching potentials leads to a situation that allows accurate predictions of metal ion discrimination by organic ligands only in a very limited range. While there are similar approximations for molecular mechanics calculations in other areas, in the field of designing metal ion selective ligands these are too severe to have molecular mechanics become a generally valuable tool. The neglect of the metal ion specific electronic effects in the metal–donor bonding interactions prevents a generally meaningful comparison of the stabilities of a series of compounds with a constant ligand set and variable metal ions. This problem is basically related to the fact that meaningful thermodynamic predictions are only possible on the basis of isomers.

There is a very similar difficulty with the computation of reduction potentials. The free energy of the reduction process may, according to a Born–Haber cycle, be arbitrarily divided into the ionization potential of the gaseous metal ion (I), the difference of the complexation free energies of the reduced and the oxidized forms in the gas phase [$\Delta(\Delta G^\circ_c)$], the corresponding aquation free energies [$\Delta(\Delta G^\circ_{aq})$] and a constant correction parameter C for solvent and electrolyte effects and the electrode setup (Eqs. (14) and (15)) [31–33]:

$$\Delta G^\circ_{red} = I + \Delta(\Delta G^\circ_c + \Delta(\Delta G^\circ_{aq}) + C \tag{14}$$

$$\Delta G^\circ_{red} = -nFE^\circ \tag{15}$$

It emerges that reduction potentials of transition metal coordination compounds depend on steric and electronic factors of the metal–donor bonding, specific solvation effects and entropic terms. These are basically the same factors which are of interest for metal ion separation, and this is not unexpected (Eq. (16), β is the Brutto stability constant):

$$E^\circ_{complex} = E^\circ_{aquaion} - \frac{RT}{nF} \ln \frac{\beta^{ox}}{\beta^{red}} \tag{16}$$

Force field calculations have been used to compute reduction potentials of hexaaminecobalt(III/II), hexaaminenickel(III/II), hexaaminenickel(II/I) and tetraaminecopper(II/I) couples, where electronic factors in each set of compounds were constant and entropic and solvation terms were shown to be linearly related to strain energy differences [32,33,41,119]. As for the computation of relative stability constants this approach may only be applied in very restrictive limits.

Approaches based on ligand field spectroscopy transition [39] and on general electrochemical parameters [34–38] do not specifically account for steric contributions (Eq. (17), S_M is a metal dependent parameter that varies with the relative metal–donor bond strength of the reduced and the oxidized forms, I_M is a metal dependent parameter that includes factors based on the ionization potential, the spherical part of the ligand field, the electrode setup and the solvation, E_L is a ligand dependent parameter:

$$E^\circ = S_M \Sigma E_L + I_M \quad (17)$$

A more generally applicable method for the computation of reduction potentials and that of relative complex stabilities (see Eq. (16)) must include both, steric and electronic contributions. This might be based on a combination of the methods based on steric energies with a variant of Eq. (17). For transition metal coordination compounds, transferable ligand field or AOM parameters [90,107,122–124] might be a first approximation for transferable electronic parameters for the metal–donor bonds.

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