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Steric Aspects of the Formation of Metal Chelate Complexes

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The geometrical and thermodynamic aspects of the formation of complexes between metal cations and organic ligands are examined theoretically from the standpoint of conformational analysis. Particular attention has been devoted to the problem of the selectivity of the complex formation, which is of practical importance. It is shown that the selectivity of complex formation is largely determined by the steric factor. The advantages and disadvantages of the available methods for the quantitative allowance for the steric factor as well as methods of calculation of the structure of coordination compounds are analysed.
The bibliography includes 105 references.

CONTENTS

I. Introduction 152
II. The steric factor in complex formation 152
III. Theoretical conformational analysis of the ligands 157
IV. Interligand interactions and the steric structure of coordination compounds 162
V. Conformational analysis of chelate rings and complexes 164

I. INTRODUCTION

The problems of the stability of metal complexes and the selectivity of complex formation are of central importance in coordination chemistry, particularly in the chemistry of complexones and extractants. Universal complexones, which are capable of binding effectively to the majority of cations in solution (in a specific pH range), have been synthesised on the basis of iminodiacetic, ethylenediaminetetra-acetic, and a number of other acids[1-3]. By virtue of their flexibility and multidentate nature, the molecules of these acids can form complexes with cations of different size. However, much more attention has been devoted recently to the synthesis of highly selective reagents capable of the selective chelation of specific cations. Numerous applications are associated with the synthesis of such reagents: in atomic industry and hydrometallurgy (extraction and separation of rare metals and radioactive isotopes), in medicine and pharmacology (the elimination from the organism of harmful metals, particularly radioactive metals, and the introduction into the organism of the essential metals—for example, iron in iron-deficiency anaemia), and in chemical industry and catalysis (the formation of complexes with a specified steric structure and with a specified stability in a particular medium).

The free energy of the binding of the metal to the ligand under specified external conditions (solvent, temperature, etc.) depends both on the metal–donor centre bond energy and on the steric structure of the ligand. In many instances of practical importance the variations in the metal–ligand donor centre bond energy are either small or are comparatively easy to take into account quantitatively. The most important factor determining the selectivity of the ligand therefore becomes its steric structure (conformation).

This review is devoted to the consideration of the influence of the ligand conformation on the selectivity of the complex formation and also of the methods for the theoretical study of the conformational possibilities and the steric structure of metal complexes. Its aim consists in summarising the hitherto few investigations in this field and in assessing the likely usefulness of the theoretical approaches to the prediction of the structures of ligands exhibiting a specified selectivity with respect to particular metal cations.

II. THE STERIC FACTOR IN COMPLEX FORMATION

1. Thermodynamic and Geometrical Conditions Governing Complex Formation in Solution

We shall consider initially certain questions of the thermodynamics of complex formation[4]. Bearing in mind that the reactions take place in solution, we can write

$$M_s^+ + L_s \rightleftarrows (ML')_s \qquad (1)$$

where M^+ is the metal cation, L the ligand, and (ML') the complex formed; the prime denotes that, as a result of its interaction with the cation, the ligand can undergo a change in its conformation, while the subscript s denotes the solvated state. In the general case L can have an integral coefficient; in addition, one cannot rule out the possibility of the addition of several different ligands to the cation.

Eqn.(1) can be given the following simple significance: the formation of the complex is equivalent to the replacement of the solvation shell and the new shell of the cation consists of the ligand molecules, which are in their turn solvated. When the free energy ΔF of the forward process in reaction (1) is negative, the equilibrium is displaced to the right, i.e. the formation of the complex is favoured by free energy factors; on the other hand, if $\Delta F > 0$, the equilibrium is displaced to the left.

In order to consider reaction (1) further, we shall divide it into several hypothetical elementary processes whose thermodynamics can be investigated in principle:

$$M_s^+ \rightleftarrows M^+, \qquad (I)$$

$$L_s \rightleftarrows L, \qquad (II)$$

$$L \rightleftarrows L', \qquad (III)$$

$$M^+ + L' \rightleftarrows (ML'), \qquad (IV)$$

$$(ML') \rightleftarrows (ML')_s. \qquad (V)$$

Processes (I) and (II) correspond to the desolvation of the cation and the ligand and are accompanied by a considerable increase of the free energy of the system ($\Delta F_1 > 0$ and $\Delta F_2 > 0$; here and henceforth we speak of the free energies of the forward processes). Process (III) is also

energetically unfavourable, because generally speaking the ligand molecule must undergo a change in its conformation on approaching an ion having a particular radius†. The free energy gain in the first three stages is compensated by energy factors favouring the formation of coordinate bonds [process (IV)] and the solvation of the complex [process (V)]. Ultimately we have for the overall process

$$\Delta F = \sum_{i=1}^{5} \Delta F_i$$

and

$$K_M^{ML} = [ML]/[M]\cdot[L] = \exp(-\Delta F/RT) \quad .$$

If equilibrium (1) is displaced to the right, one can write

$$|\Delta F_4 + \Delta F_5| > |\Delta F_1 + \Delta F_2 + \Delta F_3| \quad .$$

It is significant that the hypothetical processes (III) and (IV) are gas-phase reactions. In the calculation of ΔF_3, one can therefore use the classical methods of conformational analysis based on the model of atom–atom potential functions[5] and the influence of the solvent can be disregarded. The greatest and approximately equal in absolute magnitude are the contributions ΔF_1 and ΔF_4, which amount to $\sim 10^2$–10^3 kJ mol^{-1} and have the opposite signs. Complex formation therefore resembles a replacement of the solvation shell of the cation when it is transferred from one solvent to another with a greater solvating capacity (for example, from alcohol to dimethylformamide).

A rigorous estimation of all the contributions to ΔF requires the knowledge of the potential surfaces of the interactions of the cations, ligands, and complexes with the solvent molecules and also of the cations and ligands with one another. However, even if one imagines that such surfaces have been obtained with the aid of non-empirical calculations, the extremely complex problem of the statistical-mechanical averaging of thermodynamic functions with respect to the microstates of the system still remains. Various approximate approaches, postulating certain relations between the contributions to ΔF for specific series of ligands and cations, are therefore of interest[4]. One can imagine a situation where such relations permit the calculation of the stability constants of the complexes K_M^{ML} solely on the basis of the calculated ΔF_3 (naturally a particular model of the solvation shell must be selected for this purpose[6]).

In considering the geometrical aspects of complex formation, one may isolate three different levels of theoretical studies, each of which yields useful information about the structure and energetics of coordination compounds.

1. The study of the geometrical stabilities of isolated ligands, i.e. their theoretical conformational analysis.
2. The search for the possible distribution of the ligand donor atoms on the sphere of the central ion.
3. The study of the interaction of atoms in the complex not linked by valence bonds: (a) in chelate rings; (b) between different rings (for example, in the case of two or three bidentate ligands); (c) between chelate rings and solvent molecules (with partial retention of the solvation shell).

†Complex formation is not always accompanied by an appreciable alteration of the ligand conformation; for example, there is a possibility of the capture of a metal cation on rupture of intermolecular hydrogen bonds without significant changes in various geometrical parameters of the ligand. However, even then, by taking into account the energy of hydrogen bonding, one may speak of a contribution ΔF_3.

We shall consider each of the levels enumerated. Theoretical conformational analysis of the ligand makes it possible to discover, in principle, whether the given ligand forms a ring with the metal ion and which ions are preferable in this sense. In a macrocyclic complex one can investigate the question of the minimum and maximum sizes of the cavity. Ligands whose potential surfaces are characterised by a deep minimum corresponding to the conformer capable of binding ions with a specific radius are evidently highly selective. The selectivity of such systems is associated with the rigidity of the ligand.

If the rigidity of a bidentate ligand is defined in terms of the distance between the donor atoms, then the shorter the range within which this distance varies, the more effective the "approach" or "its failure" to the "claws" by an ion having the specified radius. This is illustrated in Fig.1, where $R_{L\ldots L}$ denotes the distance between the donor atom and the ligand calculated theoretically, l the length of the coordinate bond, and θ the LML angle. For alkali metal ions, the bond length l has been shown by experimental data to be approximately equal to the sum of the van der Waals radius of the donor atom and the crystal-chemical radius of the ion; for other metals, particularly transition metals, this bond is in general somewhat shorter (to a first approximation, its length can be assumed equal to the sum of the covalent radii of the metal and the donor atom) and can be obtained from crystal-chemical data.

It is readily seen that

$$R_{L\ldots L} = 2l\sin(\theta/2) \qquad (2)$$

or, if it is assumed that $l = R_0 + R_M$ (where R_0 and R_M are the van der Waals and crystal-chemical radii), which is usually the case for ionic bonds, we obtain

$$R_M = R_{L\ldots L}/2\ \sin(\theta/2) - R_0 \ . \qquad (3)$$

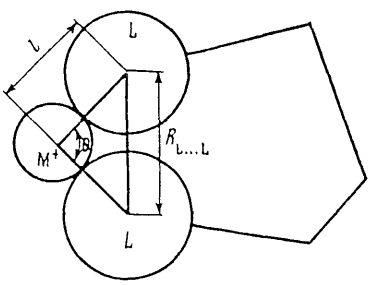


Figure 1. Schematic illustration of the formation of a chelate ring.

Eqn.(3) shows that even an absolutely rigid ligand does not determine the radius of the metal ion unambiguously; the angle θ is also significant. For octahedral or square coordination, the values of θ are close to 90°. However, it is also necessary to take into account the possibility of the deformation of θ (according to X-ray diffraction data for metal complexes, the experimental θ are in the range from 75° to 95°). If only one bidentate ligand is involved in the complex formation and the remaining sites in the octahedron (which is generally speaking distorted) are occupied by the

donor atoms of the solvent molecules, then θ should approach 90°. This happens also in the square coordination; in tetrahedral coordination the angle θ is known to be close to 109°.

In the analysis of complex formation between polydentate (in particularly macrocyclic) ligands and metal cations, the scheme in Fig.1 is unsuitable and a more detailed approach is necessary. In this instance it is apparently essential to find the optimum position of the cation by minimising the sum

$\sum_i (l_i - l_0)^2$ (*where* l_i *are the calculated cation–donor atom* distances and l_0 is the "ideal" length of the coordinate bond). If the sum remains fairly large after minimisation, then the formation of a complex is not favoured. Naturally, the optimisation procedure must be carried out for each conformation of the macroring corresponding to a fairly low energy.

The approach to the analysis of the complex formation geometry examined above is not of course the only one possible. Thus, in the chemistry of metal complexes having monodentate phosphorus ligands, the "steric parameter" θ, equal to the solid angle formed by the van der Waals spheres of different substituents at the phosphorus atom, is widely used[7]. If the Stewart–Briegleb models of ligands such as $P(OCH_2)_3CMe$, PMe_3, $P(OPh)_3$, PPH_3, P(cyclohexyl)$_3$, and P(t-Bu)$_3$ are assembled, it becomes clear that the solid angle diminishes in this series (in the case of the asymmetric ligand $PX_1X_2X_3$ the parameter θ is defined as the sum of the contributions θ_i of each X_i). Consequently the ability of phosphorus-containing ligands to form complexes with metals must fall within the above series, which is in fact observed experimentally. However, it is difficult to assess the energetics of the complex formation on the basis of the steric parameter θ.

In the next level of theoretical studies of the steric structure of coordination compounds, one can consider the interaction of the donor atoms of ligands on the sphere of the central ion (see Section IV). For this purpose, one may employ the approach, developed by Kepert[8,9], which resembles the familiar Gillespie–Nyholm "points on a sphere" theory[10] and in our case the points are not electron pairs as in Gillespie's book[10] but the donor atoms of the ligands, whose positions on the sphere of the central ion are optimised. The optimum structure of the complex and the relative stabilities of the different coordination polyhedra must evidently depend on the radius of the ion, the size of the donor atoms (or the adjacent polyatomic groups), and the number of binding sites of the ligand. Calculations within the framework of the models for the interaction of donor atoms considered below permit, firstly, the prediction of the type of polyhedron for the given coordination compound and, secondly, the selection of the starting point for the minimisation of the energy of the complex.

In the third level of investigations, as in the first, the calculations are performed within the framework of the model of the atom–atom potential functions, but here one takes into account not only the interactions within the chelate rings but also the "intermolecular" interactions between them and the interactions with the solvent molecules involved in the coordination. Conformational studies on complexes of certain transition metals with alkylenediamines and some aminoacids, which belong to the third level within the framework of the scheme considered here, have been frequently carried out by different investigators (see, in particular, the careful review by Hawkins[11]). However, the problem of the logical analysis of the steric effects with determination of the principal factors governing the stability of the complexes in solution was apparently formulated only a few years ago[4].

2. Methods for the Calculation of the Conformational Energy and Entropy of Ligands

We shall consider the problem of the conformational analysis of isolated ligands. The task is to calculate the energy as a function of independent geometrical parameters, i.e. to obtain the potential surface and to find on the latter the energy minima corresponding to stable conformers. Such information can be provided, in principle, by quantum-chemical methods—both non-empirical and semi-empirical. Taking into account the fact that the potential surfaces of metal complexes with organic ligands as well as the surfaces of the ligands themselves are multidimensional and "have many extrema", one of the requirements which must be met by the method for their investigation is a not unduly long time for machine computation of the energy. This requirement is satisfied most effectively by the method of atom–atom potential functions (AAPF) and it is not surprising that this is in fact used in the vast majority of calculations. According to the AAPF method, the energy of the molecule is represented by the sum of the contributions of non-valence, torsional, and electrostatic interactions as well as the energy of the deformation of the valence bonds and angles:

$$U_{\text{non-}\sigma} + U_{\text{tors}} + U_{\text{el}} + U_{\text{bond}} + U_{\text{angle}} \ .$$

The parameters of the potential functions have been discussed in a series of reviews[5,12–15], in particular the parametrisation for the calculations of the conformations of metal complexes has been examined[11,15]. We shall therefore consider only certain features associated with the application of the AAPF method to the conformational analysis of complexes and ligands.

As regards the parameters of the potentials of the non-valence interactions (the Lennard-Jones or Buckingham potential), the spectra of their values used by different workers are so broad that, within the framework of this review, we are unable to discuss this question in any detail. Thus modified Hill potentials[19] (p.529) have been used in the pioneer studies of Gollogly and Hawkins[16–18], who were the first to estimate the conformational energies of chelate rings. De Hayes and Busch[20,21], who calculated the conformations of five- and six-membered rings in compounds of the type M(L)Cl$_4$, where M is the metal atom [cobalt(III)] and L is ethylenediamine, trimethylenediamine, etc., using Allinger's parametrisation[22,23]. Niketić and Woldbye[24,25], who investigated trisdiamine complexes of cobalt(III), used two sets of constants for the Buckingham (6-exp) potential—those of Liquori and coworkers[26,27] and Ramachandran et al.[28]—and showed that both sets lead to approximately identical results. Finally the potentials of Scott and Scheraga[29] or Dashevskii[30,31] are most often used in the conformational analysis of peptide and depsipeptide macrocyclic complexes. We may note that all the sets of parameters of the atom–atom potentials are concerted (with the possible exception of the Liquori potential) and give rise to a good accuracy of the calculation of the conformational energies. The only important feature is that these potentials should be applied together with the corresponding sets of angular and torsional constants, since otherwise the calculation can lead to serious errors (for example, the use of the Allinger potentials requires the neglect of the 1...3 interactions and the use of spectroscopic constants for the valence angles).

The choice of the energy barrier U_0 in the expressions for the torsional potentials involves certain difficulties. Whereas the majority of investigators agree on the value $U_0 \cong 10$–12 kJ mol^{-1} for saturated C–C bonds, the values

of U_0 adopted by different investigators for bonds with a nitrogen atom and in particular for the Co–N bond in classical ethylenediamine complexes diverge significantly. It is therefore necessary to investigate the question of the influence of the uncertainty in the form of the torsional potential and in the value of U_0 on the principal calculated results, for example, on the calculated relative stabilities of the conformers. This is also true of the electrostatic component of the potential energy function (although the majority of workers who have calculated the conformations of the classical complexes were able to disregard it). The errors introduced by this component are associated with the uncertainty in the choice of parameters (the charges and the value of ε, present in the denominator of the expression for Coulomb's law and defined as the effective dielectric constant of the medium).

In the conformational analysis of ligands, the deformation energies of the valence angles and bonds can be neglected in most cases. However, when chelate rings are considered, these terms of the potential function are significant. Without taking into account the deformations of the valence angles, it is hardly possible to predict correctly the geometries and relative stabilities of different spatial isomers of involved complexes with two or three chelate rings. An important variable is also the length of the coordinate bond l. The analysis of the results of the X-ray diffraction of numerous octahedral complexes leads to the conclusion that the lengths l are minimum when $\theta = 90°$ (see Fig.1); on the other hand, when the angles θ are distorted, the increase in the length of the coordinate bond can actually exceed 0.01 nm.

The search for the optimum (or simply the stable) conformation of the complex involves the minimisation of the potential energy with respect to independent geometrical parameters, which is carried out for a specified zeroth approximation. Buckingham and coworkers[15], Busch[20], and certain other investigators have used in their calculations Boyd's program[32] based on the Newton–Raphson method and requiring the calculation of second derivatives. The advantage of this program consists in the fact that, simultaneously with the choice of direction of the one-dimensional descent, the computer yields information also about the normal vibration frequencies. In a number of other studies[24,25] the potential energy minimisation procedure was based on Wiberg's algorithm[33], the idea of which consists in selecting the direction of descent on the basis of first derivatives; the independent geometrical parameters are then the cartesian coordinates of the atoms. From our point of view, neither algorithm is entirely successful: the first requires a large amount of calculations in order to obtain the second derivatives of the conformational energy with respect to independent parameters and the second converges much too slowly near the potential minimum (furthermore, when the cartesian coordinates of the atoms are chosen as the independent variables, the function is found to be relatively insensitive to the angles of rotation). The Fletcher–Powell and parallel tangent methods as well as certain others are more successful (they are discussed by Dashevskii[5]); they do not require the calculation of second derivatives but exhibit second order convergence.

The minimisation of the potential energy with respect to independent geometrical parameters leads to the optimum geometry of the isolated ligand and yields the energy E_0 corresponding to this geometry. On the other hand, if the minimisation is carried out for a fixed value of $R_{L\ldots L}$, it is possible to estimate the energy E' of the deformed ligand (the deformation is associated with the formation of a chelate ring) and to calculate $\Delta E_3 = E' - E_0$, i.e. the contribution of the potential energy to process (III). However, this is still insufficient to estimate the contribution ΔF_3, because the calculations based on the minimisation of the conformational energy do not take into account the entropy factor.

It is noteworthy that chelation is generally speaking unfavourable on entropic grounds (naturally if no account is taken of translational entropy), since it inevitably involves the loss of one or several degrees of freedom by the ligand. The magnitude of this effect naturally depends on the conformational freedom of the isolated ligand: if the formation of coordinate bonds leads to the generation of one of a multiplicity of the possible conformers which in addition has a wide probability distribution (the potential surface of the ligand has several minima and/or these minima are fairly broad), then the free energy gain on chelation may be so large that the entropy factor is in fact the main one in determining the stability of the given complex in a certain series; on the other hand, if the ligand is fairly rigid in the isolated state, then complex formation does not alter the entropy of the system seriously.

This factor has been noted by many workers[34–38], but the methods for taking into account the entropy remained for a long time far from perfection. The first semi-quantitative estimates of the entropy of chelation were made by Westheimer and Ingraham[39], who calculated the translational entropy on substitution of two monodentate ligands by a single bidentate ligand and also the entropy of cyclisation due to the "freezing out" of internal rotations. Their main result[39] reduces to the fact that the increase of translational entropy as a result of the liberation of two solvent molecules on binding only one ligand molecule is compensated by the decrease of entropy associated with the freezing out of the internal rotations in five- and six-membered rings. However, this compensation is not always complete.

Schwarzenbach[40,41] suggested that the entropy contribution is independent of the nature of the metal ion and of the binding ligand and found that the smallest free energy gain occurs on formation of small chelate rings—a five-membered ring for a saturated bidentate ligand and a six-membered ring for an unsaturated ligand. Hawkins[11] pointed out that elementary calculation of the entropy is possible within the framework of the simple model of a one-dimensional harmonic oscillator by the formula

$$S_\xi = \Delta E/T\,[\exp(-\Delta E/RT) - 1] - R\ln[1 - \exp(-\Delta E/RT)]\ ; \quad (4)$$

where $\Delta E = (2\pi c)^{-1}(K_\xi/\mu)^{1/2}$ is the spacing of the vibrational levels, K_ξ the force constant, μ the effective mass of the oscillator, and c the velocity of light.

A much more effective calculation of the entropy of chelate complexes has been carried out by De Hayes and Busch[20], who also used the harmonic approximation but took into account the entire set of interacting oscillators, having first estimated the frequencies and modes of the normal vibrations of the complex. [We may note that the above workers[20] did not calculate the entropy of the isolated ligands, because they were interested in the contributions of the entropy factor only to the relative stabilities of different spatial isomers of cobalt(III) complexes and not to the stabilities of the complexes themselves]. In the approximation adopted, the following relation is valid for the vibrational entropy of an N-atomic complex:

$$S_{vibr} = R\sum_{i=1}^{3N-6}\{(h\nu_i/kT)/[\exp(h\nu_i/kT) - 1] - \ln[1 - \exp(-h\nu_i/kT)]\}\ , \quad (5)$$

where ν_i are the frequencies of the normal vibrations, h is the Planck constant, and kT the Boltzmann factor.

The translational and rotational entropies can be readily calculated from the formulae[42]

$$S_t = R\left[\frac{3}{2}\ln M + \frac{5}{2}\ln T - \ln p - 3.664 + {}^5/_2\right], \quad (6)$$

$$S_{rot} = R\ln[8\pi^2(8\pi^2 ABC)^{1/2}(kT)^{3/2}/\sigma h^3] + {}^3/_2 R, \quad (7)$$

where M is the molecular weight, p the pressure, ABC the product of the moments of inertia, and σ the rotational symmetry number.

Eqns.(6) and (7) do not give rise to any uncertainties because with their aid the translational and rotational entropies can be calculated exactly. However, we believe that the use of Eqn.(5) is not entirely justified, since, firstly, the configuration entropy can differ very markedly from the vibrational entropy (for example, when there are several minima on the potential energy surface) and, secondly, the vibrations may be significantly anharmonic (the form of the potential well may be far from parabolic). The attempts at a more exact calculation of the contribution of configuration entropy to ΔF_3 are therefore of interest.

It is useful to employ for the estimation of the configuration entropy of the ligands the procedures which had been used previously in the conformational analysis of dipeptides and regular polypeptides[43,45]. We shall assume that the potential energy surface of the ligand is two-dimensional and that it can be represented by a conformational map. For the configuration integral, we can then write

$$Z = \frac{1}{4\pi^2}\int_0^{2\pi}\int_0^{2\pi}\exp(-U/RT)\,d\varphi_1 d\varphi_2, \quad (8)$$

where ϕ_1 and ϕ_2 are the angles of rotation, U is the conformational energy, which is a function of these angles, R the gas constant, and T the temperature.

Having at one's disposal a procedure for the calculation of the configuration integral Z, it is possible to determine the free energy:

$$F = -RT\ln Z \quad (9)$$

(we may note that, when the configuration integral is used, no account is taken of the contribution of the kinetic energy to the free energy of the system[45,46], although to a first approximation this contribution can be neglected), the average energy

$$\langle U\rangle = Z^{-1}\int_0^{2\pi}\int_0^{2\pi} U\exp(-U/RT)\,d\varphi_1 d\varphi_2, \quad (10)$$

and the entropy

$$S = \langle U\rangle/T - R\ln Z. \quad (11)$$

Practical calculations can be carried out by replacing integration by summation over a grid. For example, we have for the free energy

$$F = -RT\ln\sum_{\varphi_1}\sum_{\varphi_2}\exp[-U(\varphi_1,\varphi_2)/RT]\,s_0, \quad (12)$$

where s_0 is the area of the elementary square ($\Delta\phi_1$, $\Delta\phi_2$). Clearly the denser the grid of the values of ϕ_1 and ϕ_2, the greater the accuracy of the calculation of the thermodynamic functions. A completely adequate accuracy is as a rule attained using intervals of 5–10° in ϕ_1 and ϕ_2 (summation outside the limits of 20 kJ mol^{-1} contours is pointless, since the contribution of such energetically unfavourable conformers to F is extremely small).

Eqns.(8)–(12) do not take into account the influence of other degrees of freedom—valence angles and bonds. However, this influence is insignificant, since the main contribution to the configuration integral comes from the torsional degrees of freedom (in exactly the same way as the low-frequency vibrations determine almost completely the vibrational partition function).

The situation is more complex when the potential surface of the ligand (or the complex) is significantly multidimensional. In this case the calculation of a multidimensional integral of type (8) is best performed by the Monte Carlo method using one of the variants of the existing selection[47]. On the other hand, if the treatment is restricted to the harmonic approximation, equations of type (5) are valid for thermodynamic functions.

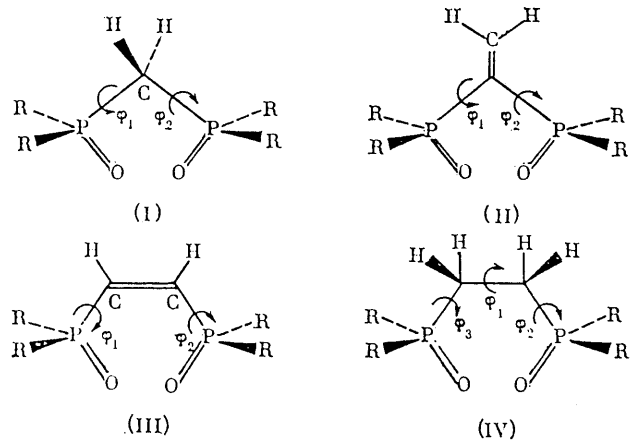


Figure 2. The valence angles and bond lengths in tetramethylmethylenediphosphine (I), tetramethylvinylidenediphosphine (II), tetramethylvinylenediphosphine (III), and tetramethylethylenediphosphine (IV) dioxides. The conformational angles are indicated by curved arrows.

The conformational entropy plays an important role in the determination of the stability of complexes of not only simple bidentate ligands but also complex polydentate ligands. The high complex-forming capacity of macrorings relative to the analogous linear systems is associated with this entropy. Thus the stability of the complex of the cyclic 18-crown-6 polyether with the K^+ ion is ~10^4 times higher than that of the analogous complex of pentaglyme $CH_3O(CH_2CH_2O)_5CH_3$, whose molecule also contains six ligand oxygen atoms[48,49]. This is in fact not surprising because the binding of the pentaglyme molecule to the ion requires the freezing out of several rotational degrees of freedom, whereas in the cyclic system certain degrees of freedom are frozen out (as a result of the ring closure conditions) even before complex formation (in the general case of an asymmetric ring the number of degrees of freedom frozen out, subject to the condition that the valence bonds and angles are fixed, is exactly six; it has been shown[50] that allowance for the ring symmetry decreases this number).

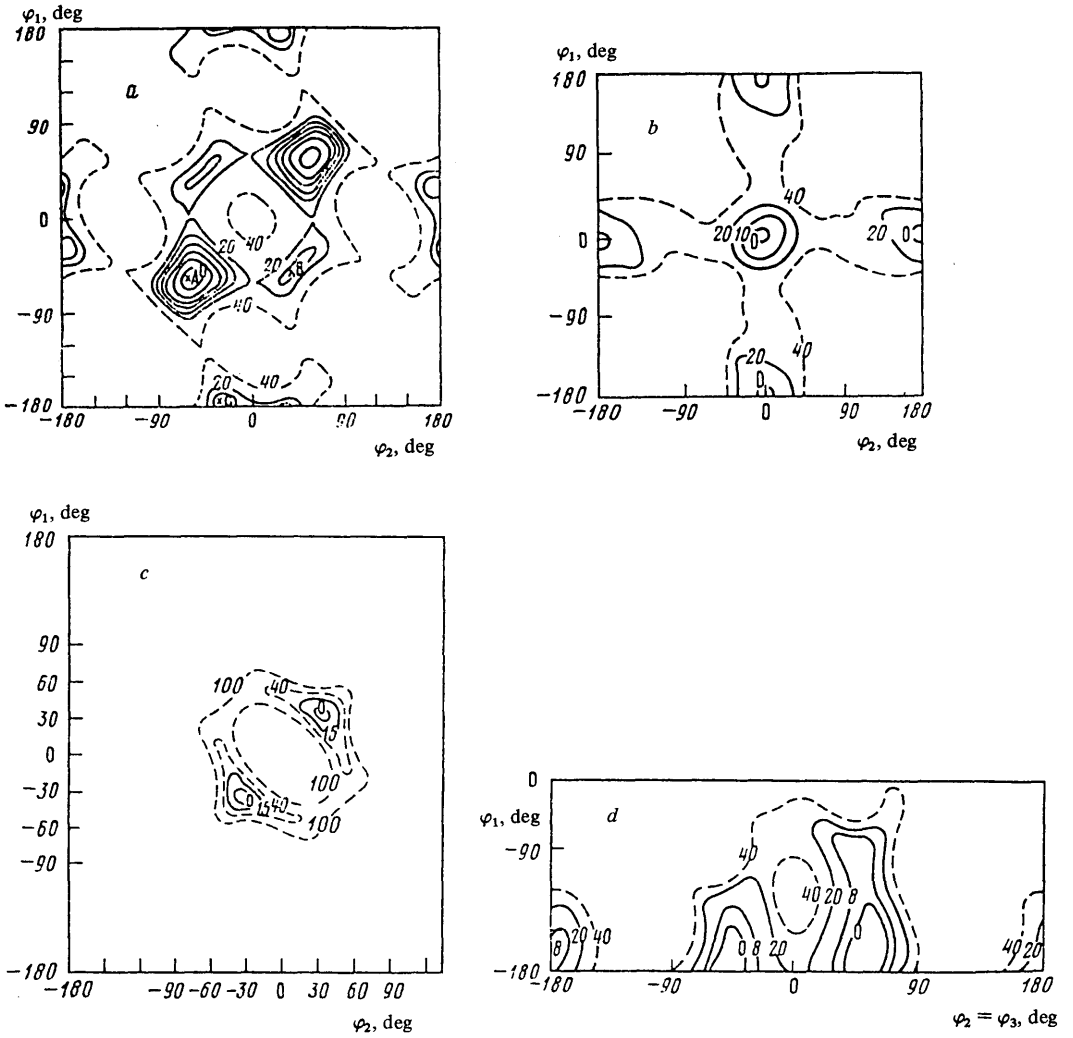


Figure 3. Maps of the conformational energies of ligands (I)–(IV) (*a*–*d* respectively) as a function of the angles of rotation ϕ_1 and ϕ_2. The numerals represent the energies in kJ mol^{-1}.

III. THEORETICAL CONFORMATIONAL ANALYSIS OF THE LIGANDS

1. Chelating Ligands

The considerations described in the previous Section show that the conformational analysis of the isolated ligands permits an approach to the estimation of the selectivity of the complex formation. In fact, if the regions of the conformational map of a rigid ligand corresponding to the required distance $R_{L\ldots L}$ are prohibited, then complex formation is impossible. Furthermore, if the ligand is not sufficiently rigid and the complex formation involves the loss of internal degrees of freedom, then the complex cannot be stable. The complexes formed by rigid ligands subject to the condition that the distance $R_{L\ldots L}$ corresponds to the energy minimum (it is best when this is a global minimum) of the isolated ligand are the most stable.

Taking into account the foregoing, we shall consider the conformational analysis and the estimation of the complex-forming capacities of several *cis*-diphosphine dioxides[51]— compounds which are believed to be highly selective extractants (the methods of synthesis of compounds of this series as well as the procedures used to study some of their properties have been described[52–55]). Although the most complete experimental data are available for the complex formation reactions of phosphine dioxides with various transition metals (many investigators[56–58] pointed out the major role of steric effects), we shall consider their interactions with alkali metal cations, which are characterised by large changes in the crystal-chemical ionic radii and hence in the steric requirements. Fig. 2 presents ligands whose conformations have been calculated within the framework of the model of atom–atom potential function[51,59]. Their choice is not fortuitous because, other conditions being equal, they contain alkylene bridges having different lengths and mobilities and connecting two functional groups. The

geometry of the molecules of compounds (I), (II), and (III) is determined by the internal rotation about the P–C bonds and only in the molecule of compound (IV) is there a possibility of additional rotation about the C–C bond.

Fig. 3 presents the conformational maps of ligands (I)–(III) (*a*–*c*) plotted as a function of the angles of rotation ϕ_1 and ϕ_2 for fixed bond lengths and valence angles and also the cross-section of the potential surface of ligand (IV) at $\phi_1 = \phi_3$ (*d*). Fig. 3*a* shows that there are three non-equivalent minima on the potential surface of ligand (I) corresponding to forms A, B and C (the first two of these have the C_2 and C_S symmetries respectively). Form A corresponds to the global energy minimum and form B represents an energy loss relative to the former of 15 kJ mol^{-1}. Form C has the open-chain (transoid) structure and is incapable of forming a chelate ring.

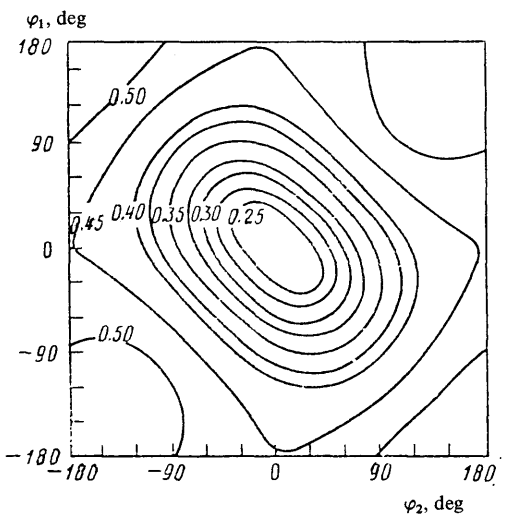


Figure 4. Dependence of the distance $R_{O...O}$ in tetramethylmethylenediphosphine dioxide on the angles of rotation ϕ_1 and ϕ_2 ("distances map"). The numerals opposite the isolines denote the distance in nm.[51]

In order to investigate the possibility of chelation, it is necessary to analyse the possible distances between the donor atoms of the ligand in order to reach conclusions on the basis of the scheme in Fig. 1 concerning a suitable radius of the cation. The "distances map" of ligand (I) as a function of the same angles of rotation ϕ_1 and ϕ_2 is presented in Fig. 4. If it is superimposed on the conformational map in Fig. 3*a*, one can discover immediately which O...O distances correspond to regions with a low energy. It is found that in conformation A the functional groups rotate in such a way that the oxygen atoms are separated by a distance of ~0.45 nm, while in conformation B they approach one another to $R_{O...O} \cong 0.3$ nm. If we now estimate the radii of the alkali metal cations by Eqn. (3) (on the assumption that θ can vary from 75° to 95° and $R_O = 0.15$ nm), we obtain $R_M = 0.12–0.18$ nm and $R_M = 0.05–0.12$ nm for conformations A and B respectively. Thus ligand (I) can form chelate rings with all alkali metal cations and in the complex with Li^+ and Na^+ it must be in the B conformation, while in the complex with K^+, Rb^+, and Cs^+ it must be in the A conformation.

The considerations described show that ligand (I) does not exhibit a high selectivity. However, this does not imply that the constants for its binding to all the cations must be the same or similar. Firstly, there exist "natural" stability series which are independent of the steric factor. Thus it is believed[3] that, in terms of the strength of binding to specific ligands, the cations of alkali and alkaline earth metals as well as the elements of the first transition period can be arranged in the series $Li^+ > Na^+ \geq K^+ > Rb^+ > Cs^+$, $Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$, and $Zn^{2+} > Cu^{2+} > Ni^{2+} \cong Co^{2+} > Fe^{2+} > Mn^{2+}$. Secondly, the appreciable deformations of the angle θ (up to 75–80° in the complex with Li^+, for example) are energetically unfavourable and lead to a lower stability of the complex. This factor is taken into account in the quasi-elastic model of the solvation shell whereby one can estimate roughly the stability constants of the complexes[6].

We shall now consider the conformational map of ligand (II) (Fig. 3*b*). In contrast to the preceding case, here there are deep and narrow potential wells, i.e. the ligand is rigid and hence also selective. One of the minima at the centre of the map corresponds to the cisoid arrangement of the P=O bonds and an O...O distance of 0.28 nm [having carried out the same calculations as for (I), it is easy to show that ligand(II) should bind preferentially to the Li^+ and Na^+ ions]. The other minima are of no interest, since they correspond to the transoid disposition of the P=O bonds which precludes the formation of a chelate ring. We may note that the selectivity of ligand (II) can be significantly increased if the hydrogen atoms of the olefinic group are replaced by bulky groups or halogen atoms. The minimum at the centre of the map then begins to resemble a deep well and the rotations of the phosphoryl groups about the equilibrium positions are extremely limited.

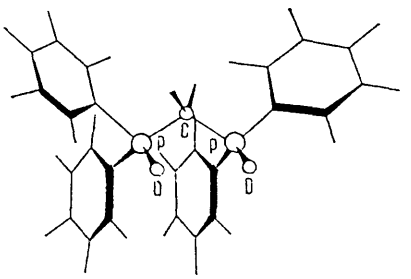


Figure 5. The optimum conformation of tetraphenylmethylenediphosphine dioxide with stacking interaction between the benzene rings[59].

The map in Fig. 3*c* shows that ligand (III) must be more selective than (I). It is significant that for this ligand only one conformation, with the C_2 symmetry, is stable while the conformation with a symmetry plane becomes unfavourable owing to the mutual approach of the oxygen atoms. As regards ligand (IV), its conformational map (Fig. 3*d*) is very "free" and the ligand cannot therefore be selective. Furthermore, one should bear in mind that the formation of the chelate ring with participation of ligand (IV) must involve the freezing out of three degrees of freedom, which is clearly unfavourable from the standpoint of entropy. Therefore, if ligand (IV) binds an alkali metal cation, only one phosphoryl group is most likely to be involved in such binding.

The conformational calculations described show that, in terms of their selectivities, ligands (I)–(IV) can be arranged in the sequence (II*) > (III) > (II) > (I) > (IV), where (II*) is a halogeno-derivative of (II). Furthermore, having analysed the positions of the energy minima and the $R_{O...O}$ distances maps, one can indicate to which cations particular ligands can be bound.

Analogous conclusions can be reached also for diphosphine dioxides of types (I)–(IV) in which the substituents in the phosphoryl group are phenyl rings and not CH_3 groups[60]. The effective volume of the phenyl rings is not only not greater but actually somewhat smaller than the volume of the CH_3 groups, since they can become readily "adjusted" to the conformation of the main chain as a result of rotations about the P–C bonds. The conformational maps of the phenyl derivatives of compounds (I)–(IV) therefore differ little from the maps discussed above. The difference consists only in the fact that the energy minima are as a rule broader and the barriers are not quite so high. It has been noted[54, 61] that the phenyl-substituted compound with a methylene bridge [compound (I)] forms much more stable complexes with certain cations than the corresponding alkyl-substituted complexes and exhibits an enhanced extractability. Calculation showed that the reason for this "anomalous" behaviour of the compounds consist in the increased stability of the conformations with parallel benzene rings (Fig.5). Such conformation is stabilised by the dispersion interaction of the rings, to which corresponds an energy of ~5–10 kJ mol^{-1} (in the gas phase). The solvent, particularly if it is non-polar, naturally can decrease significantly the above quantity, because the interaction of the benzene rings with solvent molecules can compete with the stacking interaction between the rings; furthermore, a rigid conformation is entropically more favourable than the "mixed" conformation because it causes a lower degree of "structure formation" in the solvent. Nevertheless, in many instances the conformation with parallel benzene rings (the average distance between which is 0.34 nm) is preferred.

We shall now turn to experimental data for the stability constants of the complexes of phenyl-substituted ligands (I)–(IV) with alkali metal cations[62]. These data refer to ethanol–chloroform mixtures with equal proportions of the two components and, strictly speaking, correspond to the equilibrium constants K_{MA}^{ML}, where MA is the metal acetate, and not to K_{M}^{ML}. However, the latter factor is insignificant because the free energy of formation of compounds of type MA from the metal and acetate has been shown by measurements to be the same in all cases and the values of K_{MA}^{ML} presented below therefore differ from the relevant K_{M}^{ML} by the same constant amount. The stability constants of complexes of ligands (I)–(IV) with alkali metal ions are listed below:

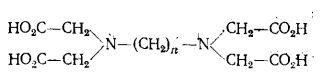
Ion	Li^+	Na^+	K^+	Cs^+
(I)	56	42	20	12
(II)	400	300	—	—
(III)	400	100	40	25
(IV)	10	8	6	7

It is easily seen that the variation of selectivity in the sequence (I)–(IV) deduced by conformational calculations agrees with the experimental trend. Ligand (II), which forms stable complexes with cations of small radius and does not form complexes with large cations, exhibits the greatest selectivity. The least stable complexes are formed, in full agreement with calculated data, by ligand (IV) and it has been established experimentally that only one phosphoryl group participates in complex formation.

Naturally geometrical analysis permits only a qualitative estimation of the relative stabilities of complexes of a series of ligands and cations. In order to obtain quantitative estimates, it is necessary to resort to additional models. In particular, if certain assumptions are made concerning the contributions ΔF_i to the free energy of formation, it is assumed that the energy of deformation of the angle θ (Fig.1) is described by Hooke's law and, after adding together the Boltzmann exponential functions, calculations of the entropy change are made on the basis of conformational maps [see Eqns.(11) and (12)], it is possible to achieve a reasonable agreement between the calculated and experimental stability constants of the complexes[6].

The same principles of the analysis of the steric structure are apparently applicable to hundreds of other ligands synthesised, which are of completely different types, ranging from bidentate to hexadentate, and whose donor atoms may be not only oxygen but also nitrogen, sulphur, phosphorus, and arsenic (we deliberately do not consider in this review complexes containing carbon–metal π- and σ-bonds, because their formation is determined primarily by electronic effects which are usually treated on the basis of the molecular orbital theory). The experimental studies in this field have reached the state where it is possible to speak of the "construction" of ligands which are bound to specific metal ions (this has been specially emphasised in an excellent review[63]) and the task of conformational analysis should be to predict the structures of the ligands.

Conformational analysis, which makes it possible to estimate not only the internal energy but also the entropy of complex formation, can explain the decrease of the stability constants of metal complexes of tetracarboxylic acids of the type



when n varies from 2 to 5 (Schwarzenbach[40]) (the entropy factor associated with the freezing out of certain degrees of freedom on formation of the complex is of primary importance here), and can also account for the topological structure[63] of polydentate chelating agents, the detailed geometry and stability of their complexes with metals, and a whole series of other facts known in coordination chemistry. Since the theory lags far behind the requirements of the experiment in this instance, the sharp increase of the number of theoretical investigations in this field and the appearance of new ideas are to be expected in the foreseeable future.

2. Macrocyclic Complexones

Among macrocyclic complexones the following have become best known: (1) tetradentate chelating agents with strong conjugation throughout the ring and an exceptionally rigid structure in the free state (porphyrins, phthalocyanines, vitamin B_{12}, corrins, and as well as their derivatives and analogues); (2) membrano-active complexones of the peptide and pepsipeptide nature, whose important characteristic is a change in the conformation of the ligand when it is bound to the metal; (3) cyclic polyethers.

The selectivity of the rigid complexones of the first class is actually determined solely by the size of the cavity within the macroring[64]. As regards the relative stabilities of the complexes of a series of ligands with different substituents,

the latter are determined by electronic factors, since the substituents exert a strong influence on the conjugation in the ring.

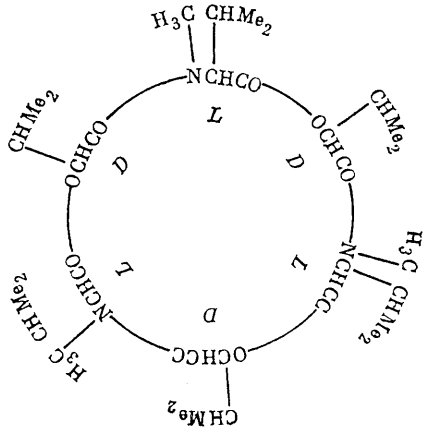


Figure 6. The structural formula of enniatin B.

Among compounds of the second class, there are membrano-active depsipeptide antibiotics such as valinomycin, enniatins, nonactin, antamanide, etc.[65]. The stability constants of the 1 : 1 complexes of three natural macrorings with the Na^+ and K^+ cations (in solution in ethanol) presented below show that the ligands exhibit an appreciable selectivity: two of these bind preferentially to the K^+ ions and one (antamanide) binds preferentially to Na^+ ions. Valinomycin exhibits a unique K/Na selectivity: in its presence the ratio of the K^+ and Na^+ fluxes through mitochondrial membranes is 10000 : 1:

Macroring	Enniatin B	Antamanide	Valinomycin
Na^+	1300	2800	50
K^+	3700	220	$26 \cdot 10^5$
References	[126–129]	[126, 130, 131]	[126, 129]

We shall consider the conformational analysis of the above compounds, which explains their high selectivity. It has been established experimentally that the molecule of enniatin B can assume two conformations depending on the polarity of the medium—the "non-polar" N and "polar" P conformations. Calculations of the conformations within the framework of the model of atom–atom potential functions[66] unambiguously predict these two structures and explain the extensive experimental data on enniatin B (infrared and Raman spectra, etc.).

The fragments of *N*-acetyl-*N*-methyl-L-valine and the dimethylamide of *O*-acetyl-*D*-hydroxyisovaleric acid, whose conformations are described by the angles of rotation ϕ and ψ about the $N-C^{\alpha}$ and $C^{\alpha}-C'$ bonds respectively, can be isolated as the structural units in the enniatin B molecule (Fig.6). Assuming that the ring has the C_{3v} symmetry and that the combination of two pairs of angles ϕ and ψ should lead to cyclic structures, it is possible to find two conformers corresponding to the energy minimum for the entire molecule: the conformer N, in which all the ester and carbonyl oxygen atoms are directed into the interior of the ring, and the conformer P in which they are all directed "outwards". Analysis of spatial models shows that the N conformer can readily bind to the K^+ ion and that a distorted octahedron made up of donor oxygen atoms is formed on the sphere of the central ion. The cavity in the N conformer is too large for the Na^+ ion, which leads to serious deformations of the macroring on binding. On the other hand, if the ions are too large compared with the cavity (Rb^+ or Cs^+), then it has been shown experimentally[65] (p.155) that sandwich structures with the 2 : 1 composition as well as 3 : 1 complexes are the most favourable.

Valinomycin is a 12-membered depsipeptide ring with 36 bonds in the main chain and an alternation of configurations of the type LLDDLLDD... There are in all 24 angles of rotation ϕ and ψ in valinomycin and it would seem, on the ground of general considerations, that less stable complexes are to be expected for this compound than for enniatin B. However, the stability constants quoted above show that this is by no means the case. The question arises of the reason for the anomalously high stability of valinomycin complexes with large cations.

An answer is provided to this question by the results of conformational calculations and the experimental data for both free valinomycin and its complexes. The search for stable conformations of valinomycin without any limitations is naturally associated with serious computational difficulties, because the potential surface has numerous extrema and simple sorting through the possible zeroth approximations would require far too long a machine computation time. Mayers and Urry[67], who carried out calculations within the framework of the model of atom–atom potential functions, therefore used the available experimental infrared and ultra-violet spectroscopic, NMR, optical rotary dispersion, and circular dichroism data for valinomycin and its complexes. They showed that valinomycin has an extremely limited set of low-energy conformations and that in non-polar solvents the "bracelet" form, stabilised by six intramolecular hydrogen bonds, is most favoured. In this form all the oxygen atoms which could, in principle, participate in complex formation are turned "outwards". Another form, also stabilised by siz hydrogen bonds but with the oxygen atoms directed "inwards" into the cavity, is less favourable according to the theoretical calculation (by 250 kJ mol^{-1}). All the remaining conformations correspond to the much more [part of Russian text missing (Ed.of Translation)].

The values presented are naturally too high because the authors[67] did not minimise the potential energy with respect to independent geometrical parameters. In fact, if the other forms possessed such a high energy, they could not have been detected experimentally. Furthermore, spectroscopic data demonstrate the existence of a whole series of forms of valinomycin stabilised by only three hydrogen bonds and also forms in which three oxygen atoms are directed "outwards" and three are directed "inwards", etc. (For a detailed discussion of the conformations of valinomycin and its analogues, see the monograph of Ovchinnikov et al.[65], pp.127–151).

Thus the exceptionally high stability of the complexes of valinomycin with large cations is apparently due to the conformational rigidity of the ligand. Despite the much smaller size of the enniatin B ring, the conformational freedom of its isolated molecule is much greater and its complexes are less stable owing to the decrease of the entropy of the system on complex formation. The selectivity of valinomycin as a complexone is determined by the consumption of the energy required for a deformation of the macroring which ensures a size of the cavity suitable for the given cation. Mayers and Urry[67] calculated the conformational energy of valinomycin as a function of the oxygen–metal distance and showed that the optimum binding should occur for K^+. Binding to a large cation (for example,

Cs^+) requires appreciable opening of the macroring, which entails an increase of the conformational energy. It is not therefore surprising that the stability constant of the valinomycin complex of Cs^+ (in solution in ethanol) is only 6.5×10^5 (compared with 2.6×10^6 for the complex with K^+).

Calculations of the geometry and energetics of certain other natural macrorings have been carried out at a higher level than in the study of Mayers and Urry[67]. The conformational calculation for nonactin[68], whose molecules selectively transfer K^+ ions through phospholipid layers and which contain 32 bonds in the main chain, is instructive. The first stage of the calculation consisted in the selection of the allowed regions of the conformational space by the hard sphere method. It was assumed that the molecule has the same symmetry S_4 as the corresponding chemical formula. Next the potential function was scanned with respect to five symmetrically independent conformational angles; for this purpose, 2×10^6 conformations, i.e. $(360/20)^5$, were examined overall, since the scanning for each angle was carried out at 20° intervals. After the minimisation of the potential function, only 7 conformations had energies within the limits of 21 kJ mol^{-1} and 39 had energies within the limits of 42 kJ mol^{-1} (if the energy of the global minimum is adopted as the zero point). It is noteworthy that all the energetically favourable conformers constitute a single family, i.e. they occupy a fairly narrow region of conformational space. The shape of the molecule then resembles a tennis ball in which there is an aperture compatible with the size of the K^+ ion. The detailed geometry of nonactin and its complex with K^+, found by Lee and Hamori[68], agrees extremely well with the results of X-ray diffraction analysis.

Another approach has been used to investigate the conformations of antamanide[69]—a macroring of approximately the same size as nonactin. Initially the antamanide molecule was subdivided[69] into fragments and low-energy conformers of the latter were selected, rejecting those which are clearly unfavourable; after this, the complete calculation was carried out taking into account all the degrees of freedom.

Synthetic polyethers of the type $(-CH_2-CH_2-O)_n$, for whose complexes with alkali metal cations numerous experimental stability constants, steric structures of the molecules, etc. are available [see, for example, Ovchinnikov et al.[65] (pp.64–78) and Refs.193–204], give rise to an interesting class of macrocyclic complexes. Theoretical studies of the conformations of these compounds and of the selectivity of their complex formation reactions so far lag behind the experimental investigations and our knowledge is limited to estimates of the dimensions of the cavities (carried out[48,70,71] by studying spatial models) and some quantum-chemical calculations[72–78]. The diameters of alkali metal cations are compared below with the dimensions of the cavity in the macroring D (the lowest value corresponds to the Corey–Pauling–Coltun model and the highest to the Fisher–Hirschfelder–Taylor model):

Cation	Li^+	Na^+	K^+	Cs^+
d, nm	0.136	0.194	0.266	0.334
Macroring	12-crown-4	15-crown-5	18-crown-6	21-crown-7
D, nm	0.12–0.15	0.17–0.22	0.26–0.32	0.34–0.43

(in the trivial names of the compounds the first numeral corresponds to the number of bonds in the macroring and the second to the number of oxygen atoms). On the basis of the data presented, the molecule of 12-crown-4 should bind more strongly to the Na^+ cation than to K^+; the following stability series should hold for the different polyethers: $Na^+ \cong K^+ > Cs^+$ for the 15-crown-5 polyether; $K^+ > Cs^+ > Na^+$ for the 18-crown-6 polyether; $Cs^+ > K^+$ for the 21-crown-7 polyether. These predictions are satisfactorily correlated with the experimental data for the stabilities of the complexes in solutions. However, in many instances certain deviations are observed, associated with the formation of sandwich structures (if the cation cannot be accommodated in the cavity, it is "clamped" between two macrorings, which results in a 2:1 "sandwich").

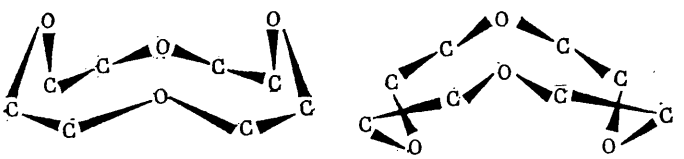


Figure 7. Schematic representation of the maxidentate (*a*) and alternate (*b*) conformations of the 12-crown-4 polyether.

We shall now consider quantum-chemical calculations of the conformations and on the energetics of the complex formation reactions of the crown ethers[72]. The conformational energies of the molecule of 12-crown-4 and the potential surfaces of the interaction of this molecule with the Li^+ ion have been calculated by the non-empirical self-consistent field LCAO-MO method in terms of the STO-3G basis. For an isolated molecule, the calculation was performed on the assumption that the C_4 symmetry (form M, maxidentate) or C_2 symmetry (form A, alternate) is retained with the standard bond lengths and valence angles (Fig.7). Subject to the limitations indicated, the only independent parameter determining the conformation of the macroring is the angle of rotation about the O–C bond χ; the remaining angles of rotation can be calculated from the symmetry and ring closure conditions.

The calculations made it possible to find the optimum value of χ for each conformer and showed that form A is more stable than form M (the energy of form A is lower by 16 kJ mol^{-1}). However, as a result of the interaction with the Li^+ ion, the maxidentate form is naturally preferable; here the equilibrium value of the angle χ in the Li^+ complex becomes different and depends on the distance d between the Li^+ ion and the centre of the molecule. Fig.8, which presents the dependence of the total energy of the system on the angle χ for three values of d, shows that the "expulsion" of the Li^+ ion to a certain distance from the plane of the macroring constitutes the optimum configuration and is apparently best when $d = 0.04$ nm. This factor as well as the deformation of the macroring on its interaction with the ion was not taken into account by Pedersen and Frensdorff[71] in their explanation of the selectivity of macrocyclic polyethers which they based on the analysis of spatial models. Nevertheless it can play a major role in complex formation (this is indicated also by data for the structure of the crystalline complex of 18-crown-6 with the Na^+ ion obtained by X-ray diffraction[79]).

It is noteworthy that the relative stabilities of the different conformers of macrocyclic polyethers predicted by calculation depend both on the method of calculation and on the parametrisation. For example, in contrast to the *ab initio* calculation examined, the CNDO/2 method predicts that form M of 12-crown-4 is favourable[76,78] and, according to Guzikevich et al.[78], the difference between energies of

forms A and M for this ether exceeds 100 kJ mol^{-1} (!). However, the CNDO/BW (Boyd–Whitehead) parametrisation leads to the conclusion that the stability of form A is higher[77]. One cannot rule out the possibility that calculations within the framework of the model of atom–atom potential functions will throw light on the problem of the relative stabilities of the conformers of crown ethers.

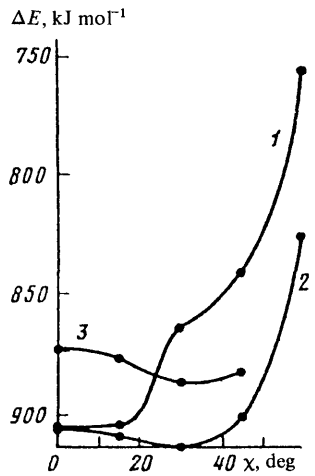


Figure 8. The energy of the interaction ΔE of the Li^+ ion with a molecule of 12-crown-4 in the conformation M as a function of χ for different values of d: *1*) 0; *2*) 0.4; *3*) 0.8.[73]

The examples examined show that both the structure of the spatial models and theoretical calculations of the conformations make it possible to explain the selectivity of natural and synthetic macrocycles with respect to specific alkali metal cations. However, for a quantitative prediction of the stabilities of the complexes, more detailed calculations are needed which take account not only of ΔE_3 corresponding to the change in the potential energy of the ligand, but also of the entropy of complex formation and of the influence of the solvent#.

IV. INTERLIGAND INTERACTIONS AND THE STERIC STRUCTURE OF COORDINATION COMPOUNDS

The steric structure of coordination compounds containing chelate rings and/or monodentate ligands is to a large extent determined by the interactions between the ligand atoms. Even if one considers simple cation–bidentate ligand complexes, these interactions also occur, because the vertices of the coordination polyhedron are occupied by the donor atoms of the solvent molecules.

The first attempt to analyse the disposition of the donor atoms on the sphere of the central ions was undertaken by Zemann[81], who examined the interaction of five point charges of the same sign on the basis of Coulomb's law.

#For the analysis of certain thermodynamic problems of chelation and macrocyclisation in solution, see Yatsimirskii[80].

Kepert[82–85] developed an approach based on allowing for the mutual repulsion of the donor atoms in the form $U_{ij} = ar_{ij}^{-n}$, where r_{ij} is the distance between atoms i and j, a a constant, and n the power exponent, which can assume values of 1 (Coulomb's law), 12 (repulsive component of the Lennard-Jones potential), or some other intermediate value (for example, 6). The energy of the complex is calculated from the formula $U = \Sigma U_{ij}$.

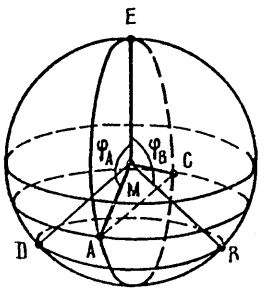


Figure 9. Schematic representation of a complex with five monodentate ligands. The metal cation M is in the centre of the sphere. The planes of the two cross-sections shown under the large circle are parallel by virtue of the pair equivalence of the ligands A, C and B, D.

We shall consider as an example the calculation of the geometry of a pentacoordinate compound with five monodentate ligands. If ligands A and C and also B and D are equivalent in pairs, the stereochemical structure of the complex can be expressed as a function of the two independent angles ϕ_A and ϕ_B (Fig.9). For $\phi_A = \phi_B$, the configuration of a tetragonal pyramid obtains; on the other hand, if $\phi_A = 90°$ and $\phi_B = 120°$ (or conversely), the configuration of a trigonal bipyramid arises.

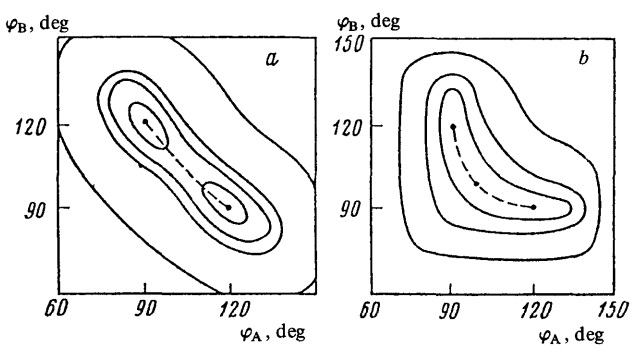


Figure 10. Contours on the potential surface (energies in relative units) of a compound M(monodentate)$_5$: *a*) for $n = 1$ in the formula of the potential $U = \sum_{i>j}\sum ar_{ij}^{-n}$; *b*) for $n = 12$.[87]

Fig.10 presents the potential surface of the coordination compound in terms of the parameters ϕ_A and ϕ_B. It is easily seen that, for $n = 1$ (i.e. when the Coulombic

repulsion of the donor atoms predominates), the trigonal bipyramid is energetically favourable, while the configuration of the tetragonal pyramid corresponds to the saddle point (Fig.10*a*). For $n = 12$ (when the repulsion of the electron shells of the atoms predominates), the last configuration becomes optimal. This calculation permits the conclusion that bulky ligands promote the appearance of the tetragonal pyramid, while ligands with residual charges on the donor atoms promote the trigonal bipyramid. However, Kepert did not reach this conclusion[82-85]. Instead he adopted the value $n = 6$, which ensured the best agreement with numerous and also extremely varied experimental data.

The value $n = 6$ found by Kepert lacks physical significance, since it corresponds to dispersion attraction with, however, the sign reversed. Examination of the interaction potentials of the donor atoms or ligands as a whole in the form of the sum of the terms with r^{-1} and r^{-12} is more realistic: if the coefficient of r^{-1} is much greater than the coefficient of r^{-12}, then Coulombic repulsion predominates; in the opposite case the geometry of the complex is determined mainly by the repulsion of the electron shells. Incidentally, there is altogether no need to employ terms with r^{-12}; the treatment can be based also on Kitaigorodskii's universal atom–atom potential[86], which depends only on the single parameter r_0. Then all calculations of this kind can be usefully performed for different values of the normalised bite of the donor atom r_0/l, (where l is the length of the coordinate bond) and for different charges on the donor atoms. In this case one other theoretical parameter has to be added (because a term of the type ar_{ij}^{-n} "is split" into two terms), but this formulation of the problem makes it possible to understand to what extent the geometry of coordination compounds is determined by electrostatic interactions and to what extent by steric hindrance.

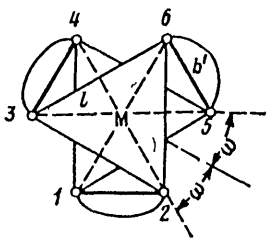


Figure 11. The view of a regular octahedron "from above". It can be represented as a prism whose upper and lower bases are rotated in opposite directions by the angle ω. The numerals denote the numbers of the donor atoms; b' is the distance between the donor atoms of one ligand.

It has been suggested[87] that a generalised dispersion-Coulombic potential, which is the sum of Kitaigorodskii's potential and the energy of the Coulombic interaction of point charges equal in magnitude, be used for the calculation of the relative stabilities of different polyhedra. The interligand interaction energy calculated with the aid of this potential is minimised on the basis of several zeroth approximations corresponding to the proposed steric structure. The possible equilibrium structures, which in the general case can differ from the ideal configuration (prism, octahedron, etc.) and determine the difference between the energies of different configurations, are then found.

The approach described has been applied to the study of the M(monodentate)$_5$, M(monodentate)$_6$, and tris(bidentate)M systems. We shall consider some results obtained[88] for the tris(bidentate)M system, which is represented conventionally in Fig.11 (the metal M is in the centre of a sphere on which the donor atoms of the ligands are distributed). It is easily seen that the configuration of the complex depends on the trigonal distortion angle ω: when $\omega = 30°$, the configuration of a regular octahedron arises and for $\omega = 0°$ that of a trigonal prism is produced; for intermediate values of the angle, the configuration is not highly symmetrical and it is usually classified as a distorted prism (it is assumed that, on distortion of the trigonal prism, both triangles shown in Fig.11 rotate by the angle ω in opposite directions relative to the "ideal" configuration with D_{3h} symmetry).

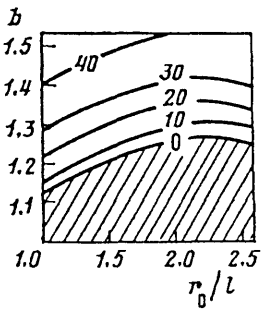


Figure 12. The equilibrium values of the trigonal distortion angle ω for different values of b and r_0/l ($q = 0.4\ e$). The isolines denote the values of the angle in degrees. The shaded regions correspond to the trigonal prism configuration[88].

The equilibrium structure of the complex must evidently be determined by purely geometrical factors (l and b', where b' is the distance between the donor atoms of a single ligand) and also by the potentials of the interaction of donor atoms (in principle, these should be the effective potentials of the interligand interaction). Calculations of the equilibrium structure were carried out for different values of the normalised bite of the ligand $b = b'/l$ and for different charges on the donor atoms ($q = 0.0\ e$, $0.1\ e$, $0.4\ e$, and $1.0\ e$) on the assumption that r_0(O...O) is 0.30 nm. Fig.12 presents a diagram indicating the equilibrium value of the trigonal distortion angle ω for different values of b and r_0/l and for $q = 0.4\ e$ (analogous diagrams were also constructed for other charges). The trigonal prism configuration corresponds to the shaded region. On the other hand, a considerable proportion of the diagram corresponds to distorted configurations—intermediate between the prism and the octahedron, a comparatively small region corresponding to the ideal octahedron ($\omega = 30°$) [in contrast to compounds of the type M(monodentate)$_6$ for which the octahedral configuration is preferred for all values of r_0/l except very low ones]. Analysis of various diagrams of this kind shows that, with increase of the charge q, the region of the stability of the trigonal prism diminishes.

On the basis of the data in Fig.12 (for $q = 0.4\ e$), we shall examine the results of the calculation of the trigonal distortion angle ω in relation to several fairly arbitrarily selected compounds (see Table). The Table shows that, despite a whole series of assumptions made in the model (for example, the assumption that all the donor atoms are distributed on

the sphere of the central ion), the agreement between the calculation and experiment is entirely satisfactory and not only for alkali and alkaline earth metal cations, whose binding is ionic, but also for transition metals, for which preferred directions of binding are frequently postulated. The points on a sphere model arises from the idea that in the ion itself there are no preferred directions and that, when they arise, this is solely due to the interaction of the ligands and their donor atoms. Whether or not this model conflicts with quantum-chemical results should be revealed by future investigations.

Parameters of the complexes.

Compound	Polyhedron	l, nm	r_0, nm	r_0/l	b, nm	ω, deg	
						calc.	expt.
$Cu\{[Me_2N]_2P(O)OP(O)[NMe_2]_2\}_3(ClO_4)_2CuO_6$	CuO_6	0.207	0.30	1.45	0.139	32	38
$Mg\{[Me_2N]_2P(O)OP(O)[NMe_2]_2\}_3(ClO_4)_2$	MgO_6	0.206	0.30	1.46	0.136	30	36
$Na[Ph_2P(O)CH_2P(O)Ph_2]_3I$	NaO_6	0.245	0.30	1.22	0.115	0	0
$Mn[MeC(O)CHC(O)Me]_3$	MnO_6	0.200	0.30	1.50	0.140	33	38
$V[MeC(O)CHC(O)Me]_3$	VO_6	0.198	0.30	1.51	0.139	32	37
$[Cu(NH_2CH_2CH_2NH_2)_3]SO_4$	CuN_6	0.215	0.32	1.49	0.130	24	24
$[Co(NH_2CH_2CH_2NH_2)_3]SO_4$	CoN_6	0.200	0.32	1.60	0.140	31	30
$[Ph_4As]_2[W(CNC(S)C(S)CN)]$	WS_6	0.237	0.39	1.64	0.131	18	14
$(Me_4N)_2[Fe(CNC(S)C(S)CN)]$	FeS_6	0.226	0.39	1.72	0.139	29	36

V. CONFORMATIONAL ANALYSIS OF CHELATE RINGS AND COMPLEXES

Calculations of the conformations of isolated ligands, whereby conclusions concerning the selectivity of the complex formation can be reached, were considered in Section III. Here we shall deal with analogous calculations for ligands bound to the metal cation by coordinate bonds. For classical ethylenediamine complexes (the $H_2NCH_2CH_2NH_2$ ligand), in which the chelate rings contain five bonds (of these two are coordinate bonds), conformational studies within the framework of the model of atom–atom potential functions were carried out by Gollogly and Hawkins[16–18,89,90]. The ideal angle θ (Fig.1) was assumed to be 90° and its deformation was described by the harmonic law with the elastic constant determined from spectroscopic data. As a result, it was shown that the five-membered ring can have two stable conformations (half-chair and envelope) and that whether or not a particular form is favourable is dictated by geometrical limitations: if the metal–donor atom bond length is less than 0.175 nm, the envelope form is preferred; for longer bonds, the half-chair form is usually realised.

The problem of the relative stabilities of the five- and six-membered chelate rings has been recently investigated[91,92], the authors having calculated the conformations of nickel(II) complexes with eight different ligands within the framework of the method of atom–atom potential functions. Among the ligands, ethylenediamine and diethylenetetramine could form five-membered rings, while 1,3-propylenediamine and dipropylenetriamine could give rise to the corresponding six-membered rings. It was found that the experimentally observed reduced stability of the six-membered rings may be fully attributed to steric strain and that the main contribution to the difference between the enthalpies of the five- and six-membered rings comes from the deformation of the valence angles and non-valence interactions.

Depending on the position of the substituent at the asymmetric carbon atom, *C*-substituted ethylenediamines can have two configurations—*R* and *S*. For each structural isomer, there is equilibrium between the λ- and δ-conformers (as shown for 1,2-diaminopropane in the *R*-configuration), in one of which (λ) the methyl group occupies the equatorial position and in the other (δ) the axial position. These conformers can be interconverted after overcoming a potential barrier whose magnitude is ~40 kJ mol^{-1} according to the measurements of the temperature dependence of the ^{13}C NMR spectra of complexes of diamines with cobalt, molybdenum, and tungsten[93].

However, not only the barrier but also the difference between the energies of the conformers is significant for complex formation. In an early pioneer study, Corey and Bailar[94] found that the λ-conformer is more stable by ~4 kJ mol^{-1}. Calculations by other workers[11], based on the minimisation of the potential energy, showed that this difference should be even smaller. According to estimates[20,21], the difference between the free energies ΔF of the axial and equatorial conformers (δ and λ for the *R*-isomer) depends mostly on the entropy contribution, which the authors[20,21] took into account within the framework of the harmonic approximation for interacting oscillators (see Section I). As a result, they obtained $\Delta F = 10$ kJ mol^{-1} and noted that allowance for the entropy leads in almost all cases to an increase of the free energy difference compared with the value of ΔE calculated by minimising the potential energy. Thus the potential well corresponding to the more "strained" δ-conformer is narrower.

Conformational analysis of the different *C*- and *N*-methyl- and dimethyl-substituted ethylenediamines as well as numerous six-membered chelate rings has been described in detail in a monograph[11]. The chair conformation of six-membered rings is the most stable; the twist-form is less favourable in almost all cases, but the presence of particular substituents can influence the difference between the energies of these forms. The problem of the stability of the axial and equatorial conformers of six-membered rings is in many respects similar to the analogous problem for substituted cyclohexanes and, since it has been thoroughly investigated, we shall not consider it.

However, we believe that the problem of parametrisation requires further study. All the workers who investigated the conformations of chelate rings assumed that the ideal value of α_0 (or the angle θ_0 if the scheme in Fig.1 is resorted to) should be 90°. Furthermore, from both the standpoint of quantum mechanics and general considerations, the presence of any preferred directions of binding at the metal atom appears doubtful. It is most likely that the angle α_0 (or θ_0) is dictated by the conditions of the environment of the metal atom (octahedral or square configuration of the metal cation) and the most direct method of taking into account the environment consists in the complete analysis of the interligand interactions on the basis of the model of atom–atom potentials. There is then no need to make any assumptions about the values of α_0 (θ_0) and the corresponding elastic constant *C*. On the other hand, in calculations on isolated chelate rings, α_0 and the constant *C* take into account implicitly the interaction of the ligand atoms with the solvent molecules, but in this approach *C* may vary on passing from compound to compound and from solvent to solvent.

In classical bistridentate complexes of cobalt(III) with ethylenediamine ligands, their derivatives, and aminoacids, the stabilities of different conformations of the chelate rings are determined in many respects by the interaction between the rings. The combination of λλλ conformations

is therefore not always energetically the most favourable. Calculations of the conformations of such complexes have been analysed in a review[15] (see also later publications[95-101]) and certain improvements to the method of calculation, consisting, in particular, in allowance for the symmetry of the complex and the conformational entropy of the ligands, have been described[102]. As a result of these improvements and also of the more accurate specification of the force field for certain fairly involved complexes, the theoretical structural parameters are almost exactly identical with X-ray diffraction data.

However, one should note that the calculation does not always yield unambiguous information about the most favourable structure. Niketič and Woldbye[24,25], who carried out exceptionally troublesome and laborious computer experiments in order to discover the possible conformers of trisdiamine complexes of cobalt(III) with three six-membered chelate rings and also similar complexes with dimethyl-substituted ligands, concluded that the situations where the potential surface contains several wells of comparable depth are typical. In solution there should therefore be equilibrium between several conformers and in the crystal (by virtue of the influence of intermolecular interactions) the most favourable conformer need not necessarily obtain. The predictions of the theory are fully unambiguous concerning the relative stabilities of the axial and equatorial conformers of different methyl-substituted derivatives and agree with experimental data.

Calculation of the relative stabilities of the conformers of involved complexes is most closely related to the problem of stereoselectivity[103]. Stereoselective reactions are understood to be those which result in the formation of two or several isomers of different chirality and one of these is present in the equilibrium mixture in a greater relative amount than the others, so that it becomes possible to isolate it by means of a series of technical procedures (in contrast to stereospecific reactions which lead to the formation of only one isomer).

The problem of stereoselectivity is too wide to be considered in the present review in any detail. We shall attempt to answer the question whether it is possible to predict theoretically the relative energies of isomeric complexes and to outline the procedures for the most effective stereoselective synthesis. In the first place one should note that the differences between the energies of the chelate rings formed by DD- and LD-ligands, for example, aminoacids, are extremely small, which is shown particularly by the results of calculations carried out by Hawkins[11] (the greatest energy difference is reached for the diastereoisomers of proline). Furthermore, the interaction with the solvent, which is usually disregarded in conformational calculations, plays a major role in determining the stability of the diastereoisomeric complexes. Finally, one must bear in mind that the intermediates formed in the reaction are not true transition states and that their energies can be regarded as proportional to the energies of the transition states only with some approximation.

Hawkins therefore viewed very pessimistically the possibility of a theoretical prediction of stereoselectivity. However, accurate conformational calculations carried out in recent years apparently have disproved this view. We may point out, in particular, studies[104,105] devoted to the conformational analysis of involved isomeric cobalt(III) complexes of glycine and alanine (the predicted[104,105] differences between the energies of the diastereoisomers were ~3–5 kJ mol^{-1}, which corresponded to a 60–80% yield of one of the isomeric forms); a satisfactory agreement with the available experimental data was achieved.

* * *

Summarising, we may note that the method of theoretical conformational analysis makes it possible to interpret and predict, on the basis of calculation of ΔF_3, the relative stabilities of metal complexes and the selectivities of the complex formation and that in many instances it is important to take into account the solvation shell, which can be done both in the continuum model and in an explicit form. In the latter case it is useful to make the calculation gradually more complex by considering in succession the conformations of the chelate ring and the interactions between the solvent molecules and/or the chelate rings. Since this problem involves many extrema when it is formulated in terms of the atom–atom approximation, the optimisation of the positions of the donor atoms on the sphere of the central ion constitutes an important auxiliary stage whereby one can find the possible zeroth approximation and predict the stereochemical configuration of the complex.

However, the calculation need not of course be carried out in this sequence in all cases. For example, the model of interacting points on a sphere has no direct bearing on complexes with macrocyclic ligands. Furthermore, in the general case certain aspects of the selectivity of complex formation can be understood simply on the basis of the conformational analysis of isolated ligands.

Theoretical studies of the stability of metal complexes and of the selectivity of complex formation are only just beginning and it must be supposed that in the near future new interesting results will be obtained in this field.

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