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Constitutional, configurational and conformational analysis of transition metal coordination complexes

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SUMMARY

A computational approach to conformational analysis is applied to the study of transition metal coordination complexes. The method provides a means of rapidly exploring conformational space without any inherent reliance on energy calculations and is therefore applicable to a wide variety of systems. It has been incorporated into an algorithm which explores the constitutional, configurational and conformational degrees of freedom for a metal ion and a number of potential ligands. The program determines which of the possible coordination complex products could form stable conformations and can therefore be used to rationalise the products obtained from the mixture. The method is illustrated using two cases: the cobalt(III)-triethylenetetramine-glycine system and complexes of diindolopyridine derivatives.

INTRODUCTION

Coordination complexes play a central role in the chemistry of the transition metals. The rich variety of oxidation states, coordination numbers and geometries available to these elements gives such complexes many applications. It would clearly be useful to be able to predict the low-energy conformations that a given complex might be able to adopt. A related problem is concerned with understanding (and thus being able to predict) the thermodynamically most stable complex(es) a metal ion could form with one or more ligands. Multidentate ligands may have a number of potential chiral centres and metals may be able to adopt a number of geometries, thus resulting in many possibilities which can be very difficult if not impossible to enumerate manually.

We have described in previous publications our investigations into the problem of performing

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computational conformational analysis, to search conformational space and locate conformations at or near energy minima [1–6]. Our objectives were to develop a means of rapidly and automatically exploring conformational space for a wide variety of molecules. We proposed that these objectives could be achieved through the application of techniques developed in Artificial Intelligence, and in particular through the judicious use of heuristics, analogous to the 'rules of thumb' employed by human experts when performing complex tasks. The approach has already been described in a number of publications and so only a brief outline is provided below, concentrating on those aspects which will be important later in the discussion and highlighting in particular those areas where heuristics are employed.

The molecule, defined by atom type and connectivity, is input either by means of a datafile produced using a molecular graphics program or using the SMILES notation [7]. In the former case any 3D coordinate information serves only to define the stereochemistry of each atom. The molecule is then analysed to recognize features such as rings, bond orders, stereocentres and aromaticity [6]. The *conformational units* present in the molecule are then determined. A conformational unit is a group of connected atoms about whose conformational behaviour the system has some 'knowledge'. Information about each conformational unit is stored in the program's knowledge base and includes details of the unit's atom types, connectivity, bond orders and stereochemistry. In addition, information is stored about the conformational behaviour of the unit. Each unit is a group of atoms whose conformational behaviour can, to a first approximation, be regarded as independent of the remainder of the molecule. For example, it is observed that a relatively small family of conformations are found for cyclohexane rings in a wide variety of molecules. The conformations which each unit adopts are stored as 3D (xyz) coordinate template files. A substructure search algorithm uses the atom type, connectivity and stereochemistry information to determine which of the units are present in the molecule.

A conformation of the molecule is generated by first assigning a conformation to each unit from among its templates. Thus, for example, the chair conformation might be assigned to a cyclohexane unit. The corresponding 3D structure of the molecule is then generated by joining together in a stepwise fashion these unit conformations. Different molecular conformations correspond to different combinations of unit conformations, the conformational space searched by the program comprising all possible combinations of unit conformations. A variety of algorithms can be used to perform this search, including the depth-first and A* methods [5]. Not every combination of templates results in an acceptable conformation of the molecule; for example, some may have high-energy steric interactions. Search efficiency is enhanced by the extensive use of checks which ensure that such unacceptable conformations are identified and rejected as early as possible.

One feature of the approach which will be relevant to the discussion below is the use of *generalized* units. It might be anticipated that a large number of units would be required to analyse a diverse set of molecules. However, many fragments show very similar conformational behaviour. For example, the conformational behaviour of many saturated six-membered rings is similar to cyclohexane. It is thus possible to use the cyclohexane unit as a model for the conformational behaviour of other related six-membered rings, such as piperidine or tetrahydropyran. If the exact units required to analyse a particular molecule are not all present in the knowledge base then the program searches for alternative units from its knowledge base whose conformational behaviour would be expected to be similar to those which are missing. For example, the cyclohex-

ane unit would initially be permitted to match only explicit cyclohexane rings (containing only sp³ carbon atoms) in the molecule. When all the units have been tried in this way, the molecule is examined to see if there are any atoms or bonds which have not been matched to an atom or bond from at least one unit. If none of the atoms or bonds are unmatched then the molecule is properly defined and the next stage of the analysis is performed. However, if there are atoms or bonds in the molecule which are not matched to an appropriate atom or bond from at least one unit then it is necessary to try and find the units from the knowledge base which will best match the missing fragments. This is done by allowing the atoms (and bonds if necessary) in the units to match a wider, more general, range of types. Thus each unit atom is first permitted to match an atom in the molecule which is in the same *geometrical class*. The geometrical classes correspond to both saturated and unsaturated variants of the common atomic geometries ('saturated tetrahedral', 'unsaturated trigonal', etc.). The carbon atoms in the cyclohexane unit would then be able to match any saturated sp³ atom in the molecule and this unit would match a piperidine ring in the molecule. Two subsequent levels of generalization are possible, if necessary [6].

Intimately linked to the generalization procedure are a number of *adjusting algorithms*. These take the conformation of each generalized unit and make small geometrical adjustments in order to produce a structure more appropriate to the atom types present in the molecule. The type of adjustment depends on the nature of the unit and the fragment of the molecule to which it is matched. Perhaps the simplest type of adjustment involves an acyclic unit in which one of the atoms has been matched to a molecule atom of the same geometrical class. Here, it is necessary simply to change the length of the appropriate bond. For example, if a carbonyl group is matched to a thiocarbonyl then the C=O bond length in the template would be changed to a value more appropriate to a C=S bond. Other algorithms deal with more detailed types of adjustment. For example, in the case where the cyclohexane unit matches a piperidine unit the bond lengths to the nitrogen will be incorrect. Here, the five atoms which correspond to the carbon atoms in the heterocyclic ring are kept in the same relative position. The coordinates of the sixth atom are then changed so that the bond lengths to its adjoining atoms are equal to the average of an ideal C–C bond and an ideal C–N bond (Fig. 1). An intermediate value is used for the bond length otherwise the angle subtended at the nitrogen deviates too much from the tetrahedral value and a high-energy structure results [8]. The adjusting algorithms enable the program to perform as well as possible in a wide variety of situations even when the exact knowledge for a particular problem is not present.

Our initial efforts were directed towards the analysis of organic molecules because the tools required to check the results (e.g. molecular mechanics programs) were readily available. However, once the validity of the approach had been established, we wished to investigate applications in other areas of chemistry for which the alternative (numerical) methods of searching conformational space frequently cannot be applied. One such extension which is reported here is in the field of transition metal coordination complexes. The conformational analysis of such molecules should be quite closely related to those found in organic chemistry and paves the way for further studies involving other types of metal-containing compounds.

THE CONFORMATIONAL ANALYSIS OF METAL COORDINATION COMPLEXES

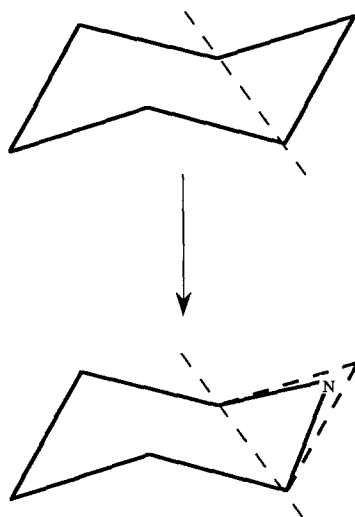There are problems applying computational techniques to the conformational analysis of

Fig. 1. Adjusting the chair conformation of cyclohexane to derive a structure more appropriate to piperidine. The five atoms which are carbon sp^3 atoms in both cyclohexane and piperidine remain fixed. The coordinates of the sixth atom are changed so that the bond lengths to the two adjoining atoms are the average value of a C–C and C–N bond. The atom remains in the plane defined by its original position and the two atoms adjoining it.

inorganic systems. Quantum-mechanical calculations, which are strongly dependent on the number of orbitals present, can be prohibitively expensive for inorganic compounds. Despite early interest in using molecular mechanics [9] the greater number of atom types which must be modelled in inorganic systems when compared to organic ones makes the development of widely applicable force fields difficult, and there is still considerable debate over the correct combination of equations and parameters to use. This is a major reason why many of the alternative methods of searching conformational space are difficult to apply in this field, due to their inherent reliance on some form of energy calculation to derive the appropriate minimum energy structure. Our approach by contrast is not dependent on any energy calculations; it generates conformations that are good approximations to the true minimum energy structures and which can be confidently used in subsequent modelling work without further refinement.

The most extensive additions required to explore the conformational space of inorganic complexes were to those parts of the program which deal with stereochemistry, as inorganic systems can show a wider variety of geometries than organic molecules. To this end, algorithms were developed to deal with the more common metal geometries not already recognized by the system: octahedral, square planar and trigonal bipyramidal. To determine how well the approach coped with these new geometries a variety of molecules were selected from the Cambridge Structural Database (CSD) [10] for analysis. Two are shown in Fig. 2 as superimpositions of suggested conformations on the appropriate crystal structures [11,12]. The RMS fits for the non-hydrogen atoms in each case are also shown in the figure. No modifications were needed to the algorithms for joining the unit conformations [2]; they operate equally well for the geometries found in inorganic systems as for those in organic chemistry.
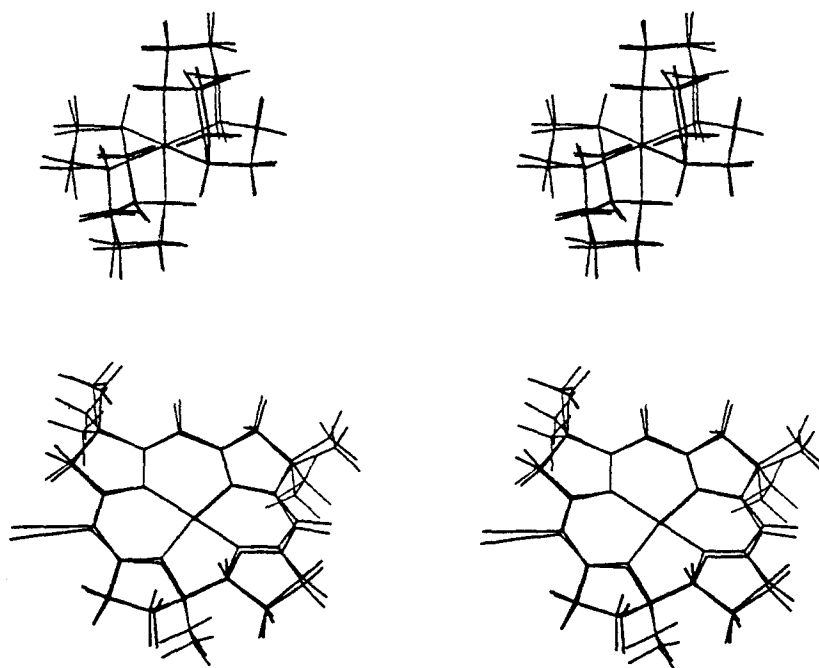
Fig. 2. Stereo diagrams of two nickel complexes to illustrate the construction of molecules containing geometries not found in organic compounds, shown as superimpositions of the theoretical and experimental structures. Top: bis(1,4,7-triazacyclodecane) Ni(II). RMS fit between theoretical and experimental structures 0.15 Å. Bottom: Ni(II) 1,8,8,13,13-pentamethyl-5-cyano-trans-corrin. RMS fit 0.16 Å.

AN INTEGRATED CONSTITUTIONAL, CONFIGURATIONAL AND CONFORMATIONAL SEARCH ALGORITHM FOR METAL COMPLEX FORMATION

Two of the characteristic features of the algorithm are its speed and its ability to operate automatically; once the molecule is defined the search proceeds without the need for any human intervention. These two features are important for applications in a number of areas. The one described here is its incorporation into a procedure for exploring the configurational and constitutional degrees of freedom of a system containing a metal and one or more potential ligands. In the test cases illustrated in Fig. 2, the algorithm was applied to a specific molecular configuration in which all the atoms have a defined stereochemistry. However, in some cases it is desired to generate *all* the unique configurations of a molecule and explore their conformational space. Such a need arises when the stereochemistry is not known or when a racemic or diastereoisomeric mixture is present. This is particularly relevant to metal coordination complexes due to the often extensive range of possible geometries and the fact that chiral centres can be introduced when the complex is formed.

The scope of such a search can be extended yet further to cover the *constitutional* degrees of freedom. The term *constitution* is used here to define a set of atoms which are bonded together in some defined fashion. We consider the metal geometry to be part of the constitution so constitutional variation arises from different coordination numbers and geometries at the metal, and

Determine the geometries available to the metal, donor atoms present in each ligand and any intra-ligand symmetry

For each coordination geometry available to the metal **do :**

> **Determine** minimum number of ligands required to fill all coordination sites
>
> **Explore** the constitutional space of this metal geometry :
>
> > **Generate** a putative complex by assigning a donor atom to each coordination site
> >
> > > **Check** the complex:
> > > Number of ligands ≤ maximum number permitted (if applicable)
> > > No donor atoms in rings > size 7 not bound to metal
> > > Molecule is not equivalent to any previously generated
> > >
> > > **If** satisfactory, explore the configurational space:
> > > **Identify** donor atoms that become asymmetric on binding to the metal
> > > **Generate** the next configuration by assigning a stereochemistry to each asymmetric donor atom and by assigning donor atoms to each coordination site
> > > **Check** that no adjacent donor atoms in a ligand are assigned to trans coordination sites
> > > **Check** that the configuration is unique
> > > **If** configuration is unique and acceptable, explore its conformational space
> > > **Until** all configurations have been considered
> >
> > **Until** all possible complexes have been generated
>
> **If** any acceptable conformations were generated, go to the next metal geometry
> **Else if** no limitation on the number of ligands is in force, go to the next metal geometry
> **Else** remove the limitation on the number of ligands that can be bound to the metal and repeat the constitutional search.

Until all coordination geometries have been examined

Fig. 3. Flow chart to illustrate the operation of the CCC program.

different donor atoms from the ligands occupying those coordination sites. In turn, each constitution will have one or more possible configurations, and each configuration may be able to exist in one or more stable conformations. The objective is thus to determine which of the possible constitutions and configurations is able to form strain-free conformations as this is invariably a necessary (but not always sufficient) requirement for the complex to be thermodynamically stable. Such information could then be used to help understand why one complex is formed in preference to another, to predict which complexes might be formed and what structures they might adopt.

It is most useful to consider the approach as comprising three nested searches. The outer loop corresponds to the constitutional degrees of freedom of the system, the middle loop to the configurational degrees of freedom of a given constitution, and the inner loop to the conformational degrees of freedom of the configuration. As a very large number of degrees of freedom may be involved, heuristic rules pertinent to the constitutional and configurational degrees of freedom are employed. These are similar in spirit to those used in the exploration of conformational space. These rules identify those constitutions and/or configurations which violate established chemical principles of metal complexes. Such constitutions and/or configurations are immediately eliminated from further consideration, thereby enhancing the efficiency of the procedure. These heu-
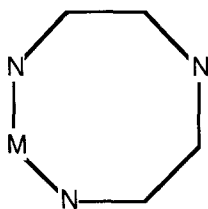
Fig. 4. An heuristic rule eliminates rings containing more than seven atoms in which a third donor atom is not bound to the metal.

ristic rules will be explained in the description of the algorithm below and are outlined in the flow chart of the CCC program in Fig. 3.

The constitutional-configurational-conformational (CCC) search program requires as input the metal ion (specified by atomic number and charge), and the individual ligand(s) (each specified via a datafile in one of a number of standard formats). Each ligand is examined to deduce which of its atoms could potentially act as a donor, forming a bond to the metal. This is done using a look-up table contained within the program. For example, ethylenediamine contains two donor atoms. For a given geometry at the metal the constitutional search then determines all ways in which the donor atoms could be assigned to the metal's coordination sites. The coordination numbers and geometries available to the metal are stored in the program's knowledge base. Symmetry in the ligand is taken into account so that, for example, the algorithm recognizes that the two nitrogen atoms in ethylenediamine are equivalent and so only one complex of the constitution $M(en)Cl_2$ would be produced. Two heuristic rules are employed at this level. The first eliminates constitutions in which two donor atoms of a multidentate ligand are bonded to the metal to form a ring containing more than seven atoms, in which there is also a third donor atom that is not bonded to the metal. This rule would eliminate, for example, constitutions in which the primary nitrogen atoms in diethylenetriamine were bonded to the metal but the secondary nitrogen atom was not (Fig. 4). The second rule is derived from the chelate effect, in that the thermodynamically most stable complexes are those with the minimum number of ligands bound to the metal and with multidentate ligands making as many bonds as possible to the metal. Initially, therefore, only constitutions containing the minimum possible number of ligands are considered. However, it will be impossible for some systems to form stable conformations which satisfy these requirements. For example, steric interactions may prevent more than one multidentate ligand from binding to the metal, the remaining coordination sites being filled by a smaller ligand such as a halide ion. Alternatively, it may be geometrically impossible for all donor atoms of a ligand to bind to the same metal. Thus both nitrogens in pyrazine cannot simultaneously bind to a single metal. Such cases are identified by the failure to construct any stable conformations. Under such circumstances, the limitation on the maximum number of ligands that can be bound is lifted and the search repeated.

To illustrate the algorithm (see also Fig. 3), consider a six-coordinate metal. With a single tridentate ligand the minimum number of ligands that can be bound with all the metal coordination sites filled is two. If a monodentate ligand is also present the minimum number is still two. However, in the case of a tetradentate and a monodentate ligand the minimum number of ligands

that can be bound such that all donor atoms are bonded to the metal is three. For the tridentate/monodentate mixture only the constitution M(tridentate)$_2$ would initially be permitted. If one or more acceptable conformations can be found for this complex no other constitution would be considered. However, if the configurational/conformational search were unsuccessful then the search would be expanded to include constitutions M(tri)(mono)$_3$, M(mono)$_6$ and complexes such as M(tri)$_3$ in which each tridentate ligand has only two donor atoms bound.

A constitution may have more than one configuration. First, it may be possible to arrange the donor atoms around the metal in more than one way. For example, there are 30 ways in which donor atoms can be assigned to the six coordination sites in an octahedral geometry. Secondly, some donor atoms may become asymmetric when bonded to the metal. For example, the secondary amino nitrogen in N-methyl ethylenediamine can exhibit R/S stereoisomerism when bound to a metal. Note, however, that neither of the nitrogen atoms in N,N-dimethyl ethylenediamine becomes asymmetric on binding. In this second case each nitrogen has two adjoining atoms which are *topologically equivalent* whereas all substituents bonded to the secondary nitrogen in N-methyl ethylenediamine are topologically unique. Donor atoms such as these which become asymmetric on complex formation are identified using the algorithm of Jochum and Gasteiger for finding equivalent atoms [13]. Donor atoms with no equivalent adjoining atoms and which adopt a tetrahedral geometry when bound to a metal will become asymmetric in the complex and are identified as such before the search procedure commences.

A configuration is first generated by assigning a donor atom to each coordination site on the metal, with a defined stereochemistry at each asymmetric donor atom. Heuristic rules are employed to reject configurations which violate established chemical principles. For example, no configuration in which a multidentate ligand has adjacent donor atoms occupying *trans* sites on the metal is permitted. Thus a configuration of M(en)$_2$ in which the nitrogen atoms of one of the ethylenediamine ligands were assigned to *trans* coordination sites in a square planar complex would be rejected at this stage. It is also necessary to eliminate equivalent configurations. For example, of the 30 possible isomers of an octahedral complex only two are unique for a complex M(en)$_3$. Some of these equivalent configurations can be identified by examining the intra-ligand symmetry (which would identify the two topologically equivalent nitrogen donors in ethylenediamine). Other equivalent configurations are found by comparing the configuration with those already discovered (as the symmetry check only considers intra-ligand symmetry it is possible that symmetrically equivalent configurations may also be generated if some of the ligands are identical). This comparison is performed using the substructure searching algorithms previously developed [6]. If the configuration is unique then the search of its conformational space is initiated. The conformational search (which is performed using the COBRA program [5]) identifies low-energy conformations of the molecule, each of which is stored on disk.

To illustrate the configurational and conformational aspects of the search, we examined octahedral complexes [CoIII(trien)(gly)]$^{2+}$. Configurational isomerism arises from the different arrangements of the two ligands around the metal, and from the two secondary amino nitrogens in triethylenetetramine which become asymmetric when bound. A total of 24 unique configurations are possible. However, for only 10 configurations were acceptable conformations obtained; these 10 configurations comprise five pairs of enantiomers which are schematically illustrated in Fig. 5. They fall into three general families as indicated: the s-*cis*, uns-*cis*$_1$ and uns-*cis*$_2$. The preparation of all 10 configurations has been described and five different crystal conformations

s-cis

uns-cis₁

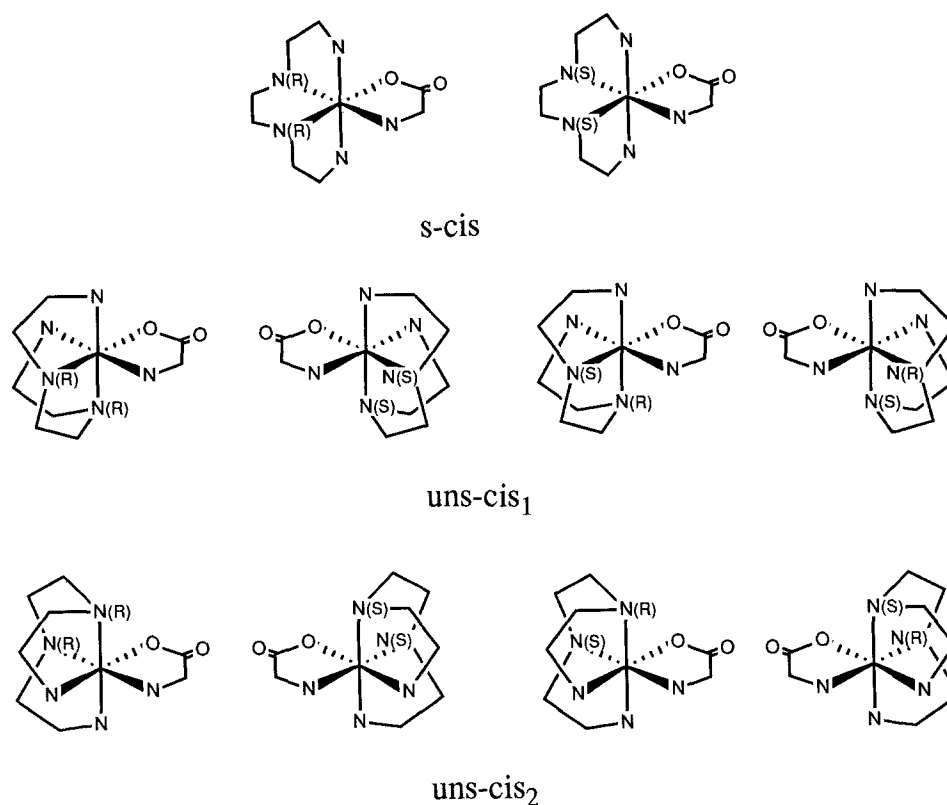

uns-cis_1

uns-cis_2

Fig. 5. The 10 different configurations possible for the complex formed between octahedral cobalt (III), triethylenetetramine and glycine.

have been reported [14–16]: two of the (RS)uns-cis_2, and one each of the (RR)uns-cis_1, (RS)uns-cis_1 and (RR)s-cis. Conformations corresponding to all five were among those obtained from the search, with RMS fits between theoretical and experimental structures all less than 0.1 Å. The entire search (which required approximately 40 s on a Silicon Graphics Indigo workstation) thus correctly identifies the existence of 10 different configurations and predicts possible structures which include those observed in the solid state and also a number of plausible alternatives.

COMPUTATIONAL STUDIES OF TRANSITION METAL COMPLEXES OF DIINDOLO-PYRIDINE DERIVATIVES

The CCC search algorithm was subsequently employed to study transition metal complexes with diindolopyridine-based ligands. Diindolopyridine (Fig. 6) has an extended aromatic system and as such its fluorescence spectrum might be expected to show a characteristic change when bound to a metal. As fluorescence measurements are very sensitive, such ligands have potential applications in detecting low metal concentrations as is required in areas such as pollution monitoring. A number of derivatives of diindolopyridine have been prepared [17] and their
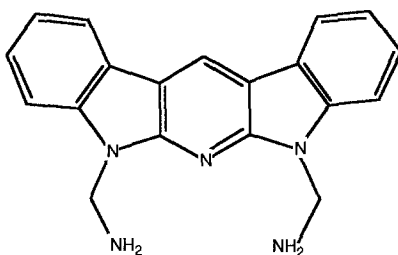
Fig. 6. Diindolopyridine.

complexation behaviour with a variety of metal ions investigated, including structural studies using single crystal X-ray diffraction [18]. The computational techniques described above were concurrently applied to these systems in order to understand the observed chemical and structural behaviour and to assist in planning the synthetic work.

To perform a conformational search, COBRA must be supplied with the necessary knowledge, in the form of conformational units and the associated 3D templates. The templates for each unit are typically derived by analysing experimental data from X-ray crystallography or by calculation. For the $[Co(trien)(gly)]^{2+}$ system two units were used to construct the various configurations: an M(en) unit and an M(gly) unit, in both of which the metal adopted an octahedral geometry. The conformations were derived from the abundant crystallographic and theoretical studies of such complexes. To analyse diindolopyridine complexes, conformational units corresponding to the six-membered ring indicated in Fig. 7 were required, in addition to the units already present in the knowledge base such as benzene and pyrrole rings. A substructure search of the Cambridge Structural Database found just two metal complexes containing this particular fragment or any obviously related to it, which was not considered a sufficiently large sample for any reasonable conclusions to be drawn. It was therefore necessary to resort to other methods to derive the necessary templates. The lack of specific experimental data and of force fields appropriate to such systems meant that a degree of chemical intuition was required to determine the accessible conformations. For the six-membered ring shown in Fig. 7 there are a number of constraints that can reasonably be imposed on possible structures. First, the N=C–N–C fragment would be expected to be planar due to delocalisation. Secondly, maximum overlap between the nitrogen lone pair and the metal would be obtained if the metal lies in the plane of the pyridine ring. Experimental evidence to justify this second assumption was sought from the CSD; the program
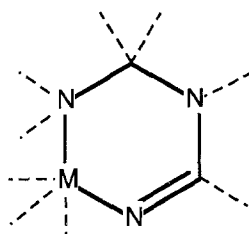

Fig. 7. Conformational unit required to analyse complexes containing diindoloypyridine. In addition to the 5-coordinate metal shown, other metal geometries would also be required.
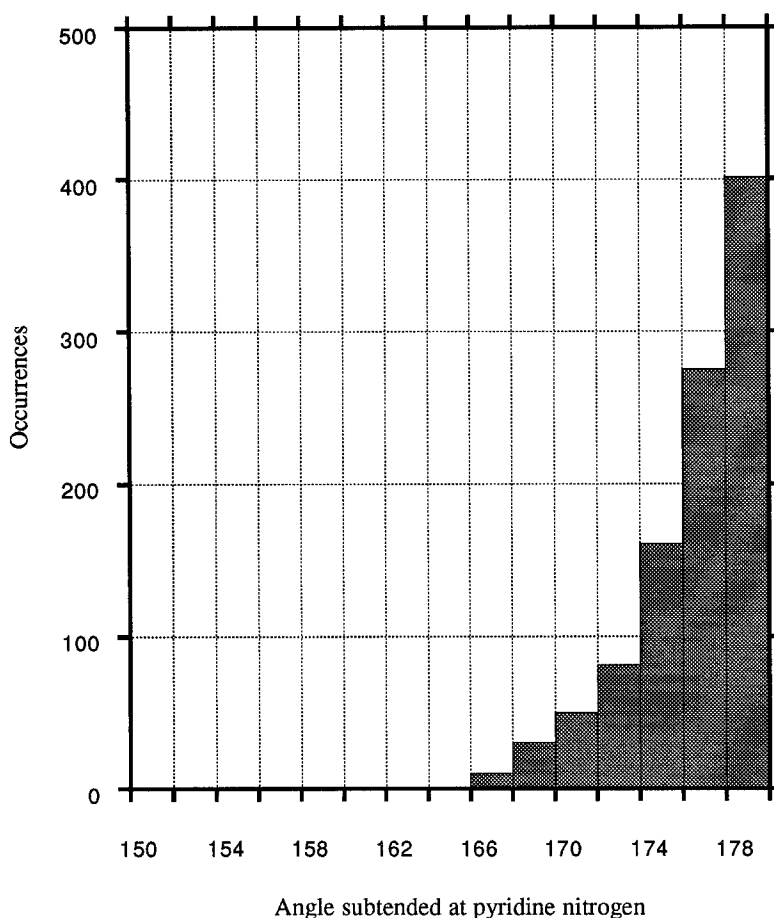
Fig. 8. Results of Cambridge Structural Database search: histogram showing the distribution of angles M–N–C subtended at the nitrogen for all compounds containing a single metal bonded to a pyridine.

QUEST was used to identify all crystal structures of complexes containing a pyridine ring bound via the nitrogen to a transition metal. The search was restricted to complexes containing just a single metal, to avoid effects due to metal–metal bonds. The angles subtended at the nitrogen by the metal and the carbon atom at the 4 position in the pyridine ring were calculated using the GSTAT program for the 539 compounds found. The fragment occurs 1010 times and Fig. 8 shows the distribution of angles. As can be seen, there is a clear preference for such compounds to have the metal–nitrogen bond in the plane of the pyridine ring.

Five of the six atoms in the ring are coplanar if these two constraints are satisfied. The sixth atom (the amine nitrogen) could therefore lie in this plane or on either side of it, a total of three possible conformations for a given angle at the metal. Three distinct angles can be subtended at the metal with the current tetrahedral, square planar, trigonal bipyramidal and octahedral geometries: 90° (in octahedral, square planar and trigonal bipyramidal geometries), 109.5° (in tetrahedral geometries) and 120° (in trigonal bipyramidal geometries). For angles of 90° and 109.5°

it was possible to construct two conformations in which there was little deviation from standard bond lengths and angles. These correspond to conformations in which the amine nitrogen is out of the plane of the ring. The third (planar) structure is, however, distinctly strained (i.e. bond lengths and angles deviated significantly from their ideal values) and thus would be expected to be unstable with respect to the other two forms. Unstrained conformations could only be generated for metal angles of 90° and 109.5°; in the case of trigonal geometries a significant distortion of the ring was needed to maintain the angle at the metal. Consequently, no unit was added to the knowledge base with a N–M–N angle of 120°. Units in which the angles at the metal were 90° and 109.5° were thus added to the knowledge base, with two templates per unit. Only a single unit was defined for each unique metal geometry as the metal–nitrogen bond lengths for both pyridine and amine donors for the metals we wished to consider were very close in value [19] and so the conformational behaviour of the six-membered ring fragment was expected to be very similar for the various metals. These units thus served as a starting point to derive structures for the other metals via the generalization and adjusting algorithms.

A variety of diindolopyridine derivatives were synthesized, including 5,7-bis(dimethyl)-diindolopyridine, 5,7-bis(pyrrolidylmethyl)diindolopyridine and 5,7-bis(morpholinomethyl)diindoopyridine. The constitutional/configurational/conformational space of each of these ligands with a variety of metals (Ni(II), Co(II), Co(III), Cu(II) and Pd(II)) was investigated. In all cases a two-component ligand mixture was assumed, one component being the diindolopyridine derivative and the other a halide anion (chosen to be chloride). The geometries which each metal ion was permitted to adopt are shown in Table 1; these were based on those found in standard texts [20].

For each metal geometry, similar results were obtained for all the metal ions investigated and can be summarized as follows. For octahedral geometries stable conformations were obtained for the constitution $MLCl_3$ (L≡diindolopyridine derivative). No constitutions of the form ML_2 were obtained due to high-energy steric interactions between the ligands. For trigonal bipyramidal geometries, complexes $MLCl_2$ were obtained, though only for configurations in which the angle subtended by the diindolopyridine ligand at the metal was 90°. For square planar and tetrahedral geometries complexes stable conformations were obtained for constitutions of the stoichiometry MLCl.

A variety of crystals suitable for X-ray crystallographic studies were obtained. In some instances cleavage of the ligand was observed; such situations are beyond the scope of the computational approach at present and are not considered here. In three cases the expected complexation reaction was observed: Co(II) with the bisdimethyl derivative, Cu(II) with the

TABLE 1

GEOMETRIES PERMITTED TO EACH OF THE METAL IONS WHOSE COMPLEXATION BEHAVIOUR WITH DIINDOLOPYRIDINE DERIVATIVES WAS INVESTIGATED

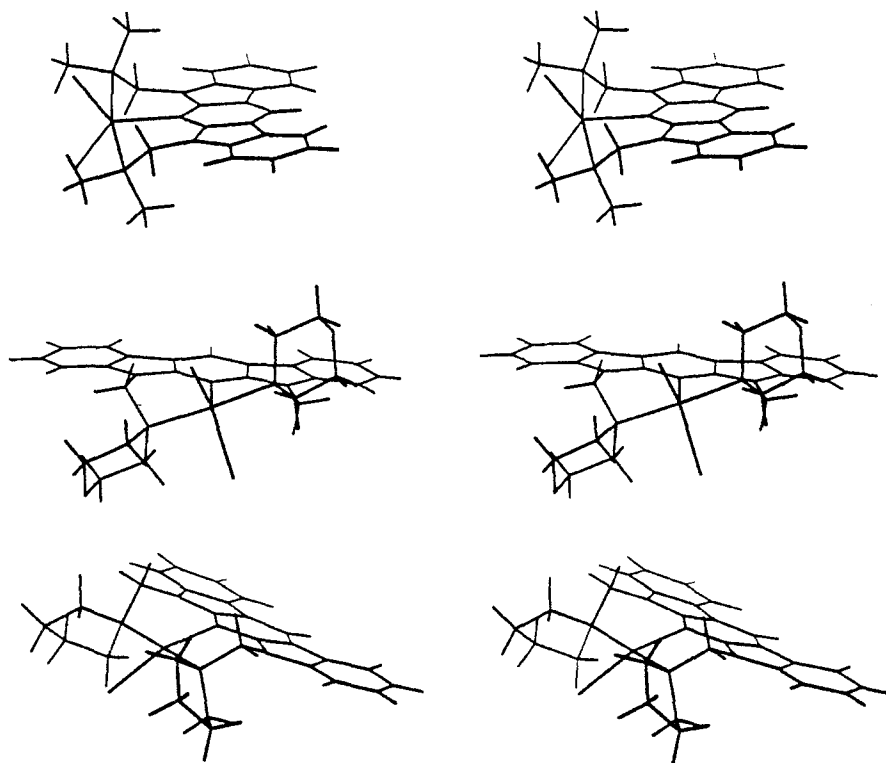| Metal ion	Geometries permitted
Co(II)	octahedral, trigonal bipyramidal, square planar, tetrahedral
Co(III)	octahedral
Cu(II)	octahedral, trigonal bipyramidal, square planar, tetrahedral
Pd(II)	octahedral, trigonal bipyramidal, square planar

Fig. 9. Stereoview of crystal structures of the cobalt, copper and palladium complexes of diindolopyridine derivatives (see text).

bis(morpholinomethyl) derivative, and Pd(II) with the bis(pyrrolidylmethyl) derivative. The experimental X-ray structures of these complexes are shown as stereo pictures in Fig. 9. The Co(II) and Cu(II) complexes both adopt trigonal bipyramidal geometries whereas the Pd(II) complex adopts a distorted square planar geometry. In the first two cases the geometry of the relevant conformation suggested by the CCC procedure was within 0.25 Å RMS of the true crystal coordinates. In the latter case, however, there is a significant difference between the predicted conformation and that observed. This is due to the distorted nature of the square planar geometry at the metal in the experimental structure and the non-coplanarity of the pyridine ring, the angle subtended at the nitrogen by the palladium and the 4-carbon being 153°.

DISCUSSION

This paper has described the application of a computational approach for exploring conformational space to metal coordination complexes, and its incorporation into an algorithm for exploring the configurational and constitutional degrees of freedom of a metal and a set of ligands. In all three aspects of the search, heuristic rules are employed to enhance the efficiency of the search, by eliminating constitutions, configurations and conformations which violate established chemical principles. The search is designed to identify those complexes which might form energetically

favourable conformations, and could thereby help to identify the thermodynamically plausible product(s). Such information has direct application in the design of ligands to interact with specific metals. It should be emphasized that many factors are not taken into account by the search procedure described here. For example, no account is taken of ligand-field stabilisation energy. However, the approach does provide a means of rapidly identifying plausible complexes and it provides good-quality conformations which may act as starting points for more detailed calculations using quantum mechanics, molecular mechanics minimization or molecular dynamics.

As is clearly demonstrated by the study of diindolopyridine complexes, the quality of the predicted structures is crucially dependent on the knowledge incorporated into the system. The results for the copper and cobalt complexes are in agreement with those determined experimentally but the outcome is not so satisfactory for the palladium derivative. This highlights a potential problem with knowledge-based approaches: their performance is limited by the information contained within them. One advantage of a knowledge-based approach to conformational analysis and search is that the amount of data required to derive the necessary knowledge can be significantly less than is needed to parameterise the force field models that are integral to alternative methods. As indicated above, there are two sources that have been used to derive the structural knowledge that is required: experimental data (primarily crystal structures) and calculation. Force fields have been extensively used to derive templates for use with organic systems, but for inorganic molecules the currently available force fields are not so well developed and it is often necessary to rely solely upon the results of X-ray crystallography. The templates for a given unit are typically obtained by identifying molecules from the database which contain the unit and then classifying its conformations using a variety of analysis methods. However, when there is insufficient data (as in the present case) it may be necessary to use an element of chemical intuition allied to appropriate examination of any relevant data that is available.

The CSD was thus re-examined to see if further light could be shed on the problem of the palladium complex. 202 molecules are present in the CSD for the fragment in Fig. 10, subject to the requirement that only a single metal is present. In these molecules the fragment occurs 496 times. In seven of the compounds the angle at the pyridine nitrogen is less than 160°. Only one of these seven compounds is particularly relevant to the present discussion: dichloro-(8,8'-bis(aminomethyl)-2,2'-biquinoline-N,N',N'',N'''')-manganese(II), a six-coordinate complex with a tetradentate ligand in which the angles at the pyridine nitrogens are 157° and the metal–N(pyr)
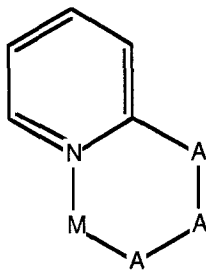

Fig. 10. Fragment used to examine the CSD in the analysis to find metal complexes containing fragments also present in diindolopyridine complexes. The atom, M, was permitted to match any transition metal; the atoms, A, could match any non-hydrogen atom. Bond orders between A–A and C–A bonds were permitted to match any order; the bond M–A was required to match a single bond.

bonds are 2.285 Å. In contrast, the Pd–N(pyr) bond is 2.089 Å. In retrospect, a case could perhaps be made for explicity including a template in which the metal is not coplanar with the pyridine ring, but as shown in Fig. 8 it would be incorrect to use such a conformation for most systems containing a metal–pyridine bond. One way to tackle such a problem might be to develop rules which deal with the 'special cases' and 'exceptions'. Such an approach has been employed in other systems, but they frequently suffer from the drawback that there will always be some problem for which no rule is applicable. This was also found to be the case when attempting to devise rules to deal with the resolution of intramolecular strain in organic compounds [21]. A large number of increasingly complex rules were needed for each circumstance. A better approach was to devise a small number of general rules which would be applicable to all types of problem [3,21]. It may be possible to develop analogous methods to deal with the different types of 'strain' which are found in coordination complexes and organometallic compounds (e.g. the electronic configuration of the metal) and thereby improve the predictive ability of the approach.

ACKNOWLEDGEMENTS

REFERENCES

1 Dolata, D.P., Leach, A.R. and Prout, K., J. Comput.-Aided Mol. Design, 1 (1987) 73.
2 Leach, A.R., Prout, K. and Dolata, D.P., J. Comput.-Aided Mol. Design, 2 (1988) 107.
3 Leach, A.R., Prout, K. and Dolata, D.P., J. Comput. Chem., 11 (1990) 680.
4 Leach, A.R., Prout, K. and Dolata, D.P., J. Comput-Aided Mol. Design, 4 (1990) 271.
5 Leach, A.R. and Prout, K., J. Comput. Chem., 11 (1990) 1193.
6 Leach, A.R., Dolata, D.P. and Prout, K., J. Chem. Inf. Comput. Sci., 30 (1990) 316.
7 Weininger, D, J. Chem. Inf. Comput. Sci., 28 (1988) 31.
8 Leach, A.R., The Application of Artificial Intelligence Techniques in Conformational Analysis, D. Phil. Thesis, University of Oxford, 1989.
9 Corey, E.J. and Bailar, J.C., J. Am. Chem. Soc., 81 (1959) 2620.
10 Allen, F.A., Bellard, S.A., Brice, M.D., Cartwright, B.A., Doubleday, A., Higgs, H., Hummelink, T., Hummelink-Peters, B.G., Kennard, O., Motherwell, W.D.S., Rodgers, J.R. and Watson, D.G., Acta Crystallogr., B35 (1979) 2331.
11 Zampa, L.J. and Margulis, T.N., Inorg. Chim. Acta, 45 (1980) L263.
12 Dunitz, J.D. and Meyer, E.F., Helv. Chim. Acta, 54 (1971) 77.
13 Jochum, C. and Gasteiger, J., J. Chem. Inf. Comput. Sci., 17 (1977) 113.
14 Buckingham, D.A., Dwyer, M., Gainsford, G.J., Ho, V.J., Marzilli, L.G., Robinson, W.T., Sargeson, A.M. and Turnbull, K.R., Inorg. Chem., 14 (1975) 1739.

15 Anderson, B.F., Bell, J.D., Buckingham, D.A., Cresswell, P.J., Gainsford, G.J., Marzilli, L.G., Robertson, G.B. and Sargeson, A.M., Inorg. Chem., 16 (1977) 3233.

16 Buckingham, D.A., Cresswell, P.J., Dellaca, R.J., Dwyer, M., Gainsford, G.J., Marzilli, L.G., Maxwell, I.E., Robinson, W.T., Sargeson, A.M. and Turnbull, K.R., J. Am. Chem. Soc., 96 (1974) 1713.

17 Phillips, H.E. and Peach, J., personal communication.

18 Jackson, B.K., Humphreys, V.M.M., Smith, A. and Prout, K., personal communicaton.

19 Orpen, A.G., Brammer, L., Allen, F.H., Kennard, O., Watson, D.G. and Taylor, R., J. Chem. Soc. Dalt. Trans., (1989) S1–S83.

20 Cotton, F.A. and Wilkinson, G., Advanced Inorganic Chemistry, 5th ed., John Wiley and Sons, New York, 1988.

21 Dolata, D.P. and Carter, R.E., J. Chem. Inf. Comput. Sci., 27 (1987) 36.

22 Ferrin, T.E., Huang, C.C., Jarvis, L.E. and Langridge, R., J. Mol. Graphics, 6 (1988) 13.