Computer Simulation Studies on Metal-Ionophore Interactions

A

thesis submitted

in partial fulfillment of the requirement of the degree of

Master of Science

in

Chemistry

Under the supervision of

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Submitted By

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Karamjeet Kaur

Date : June 11, 2009
Place: Patiala

KARAMJEET KAUR

Candidate's Declaration

I, hereby declare that the work being presented in the thesis entitled **"Computer simulation studies on metal ionophore interactions"**, in partial fulfillment of the requirements for the award of the degree of Masters in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala, is my own work during the period of Jan 2009 to May 2009, under the supervision of Dr. Susheel Mittal, Professor, School of Chemistry and Biochemistry, Thapar University, Patiala. I have not submitted the matter embodied in this thesis for the award of any other degree.

Patiala
Date: 11/6/09

Karamjeet Kaur
Karamjeet Kaur

This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

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Dr. Susheel Mittal
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(Supervisor)

Susheel Mittal 11.6.09
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Head of School of Chemistry & Biochemistry

Certificate

This is to certify that the thesis entitled **"Computer simulation studies on metal ionophore interactions"**, being submitted by Ms. Karamjeet Kaur in partial fulfillment of the requirements for the award of degree of Master of Science in the School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonifide work carried out under the supervision of Dr. Susheel Mittal and that no part of this thesis has been submitted for the award of any other degree.

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Introduction

There is a growing interest in designing and synthesizing macrocyclic ring systems that display selectivity in binding to guest substrates. Such studies have been motivated both by practical applications and the scientific challenge of understanding how certain host molecules “recognize” guest substrates. The range of conformations accessible for complexation must be understood for characterizing the conformational features responsible for host-guest recognition and selectivity. Molecular Modelling with the help of different softwares is just another step in this field.

Molecular modelling

Molecular modelling is a collection of (computer based) techniques for deriving, representing and manipulating the structures and reactions of molecules, and those properties that are dependent on these three dimensional structures.

Molecular modelling is a collective term that refers to theoretical methods and computational techniques to model or mimic the behaviour of molecules. The techniques are used in the fields of computational chemistry, computational biology and materials science for studying molecular systems ranging from small chemical systems to large biological molecules and material assemblies. The benefit of molecular modelling is that it reduces the complexity of the system, allowing many more particles (atoms) to be considered during simulations.

What are Computer Models?

They are basically mathematically representations/models of molecules and properties such as:

- Atomic positions (cartesian coordinates, internal coordinates - bond lengths, angles, and torsions)
- Molecular surfaces are mathematical functions based on atomic position and atomic radii
- Energies are sets of equations involving atomic distances, atom type, bonding arrangement, etc

Advantages of Computer Models

1. Geometrically accurate (only limited by knowledge)
2. Capable of precise manipulation
3. Conformational energies may be calculated (QM and MM)
4. Readily superimposed (compare conformations, properties, volumes, etc)
5. One molecule may be positioned precisely with respect to a set of spacial requirements (enzyme - substrate, activated complex, etc)
6. Easily and conveniently stored, edited, and duplicated

Basically modelling aids in understanding and prediction of molecular phenomena.

To study the interactions of ionophore metal complexes there are different softwares and techniques available like:

AMBER	MD, MM, FEP
SHAKE algorithm	(CHARMm).
CPK models	Quantum CAChe
Hyper Chem	Scigress, MOPAC etc

CAChe

A cache is a temporary storage area where frequently accessed data can be stored for rapid access. Once the data is stored in the cache, future use can be made by accessing the cached copy rather than re-fetching or recomputing the original data, so that the average access time is shorter. Cache, therefore, helps expedite data access that the CPU would otherwise need to fetch from main memory.CAChe offers computational applications based on classical mechanical and quantum mechanical models.

Quantum CAChe

Quantum CAChe (Computer Aided Chemistry) and the associated Project Leader software produced by Oxford Molecular are small molecule modelling packages capable of molecular mechanics and semi-empirical quantum mechanics calculations among others. With this software it is possible to investigate a wide range of molecular

properties such as partition coefficients, reaction energy profiles, transition state geometry, UV and IR spectra as well as the more usual molecular mechanics calculations such as optimized geometry and conformational analysis. Included is the capability to construct interactive graphs from numerical results.

Computational chemistry and CAChe for Windows

CAChe for Windows is a computer-aided molecular design (CAMD) modeling tool for the Microsoft® Windows 98, XP, 2000 operating systems. CAChe for Windows enables you to draw and model molecules and perform calculations on a molecule to discover molecular properties and energy values.

Introduction to computer-aided chemistry

- Computer-aided chemistry enables us to create a model of a molecular structure on a computer. We create the model by drawing it, importing it from another program.
- The model can be moved around the x, y, and z axes of the computer screen, and view the structure from many different angles and perspectives.
- The molecule can be displayed as a simple line drawing, as three dimensional spheres and cylinders, or as a combination of many different modeling styles.
- The experiments in computer-aided chemistry use mathematical models derived from computational chemistry to calculate molecular properties and geometries.

The following illustration shows a molecule before and after a CAChe for Windows optimization experiment to lower the steric energy of the molecule using calculations from classical mechanics.

Fundamental Aspects

Molecular mechanics is the application of classical mechanics to molecules. Classical mechanics is used to describe the motion of macroscopic objects. In molecular mechanics, atoms are treated as spheres whose mass depends on the element. Chemical bonds are treated as springs whose stiffness depends on which elements are bound together, and whether the bond is single, double, or triple. Other types of springs are used to model changes in bond angles, dihedral angles, etc. Each of these various types of springs will have spring constants associated with them. Experimental and theoretical methods are used to determine these parameters. Additional equations from classical physics, such as Coulomb's Law, are used to handle any electrostatic interactions present within a molecule. The sum of all energy terms that apply to a particular molecule are added together to define what is called the "steric" energy, or total potential energy, of the molecule. All of the equations and associated parameters used to calculate each energy term are collectively called the "force field". Different force fields have been developed for different molecular types (e.g. small organic molecules vs. large biomolecules).

Applications

In computational terms, molecular mechanics is the least expensive (fastest) method. It is especially well suited for providing excellent structural parameters in terms of bond distances, angles, etc., for the most stable conformation of a molecule. This so-called "geometry optimization" is often used as the first step before a calculation of another type is performed. This is done to insure that the molecule is in it's lowest energy state so that calculated results can be compared to those done experimentally.

Molecular Mechanics Methods

For organic molecules with a variety of functional groups, there are two widely used methods known as MM2 and MM3. The MM2 method is a precursor of MM3. The parameters used in these methods were chosen to reproduce the experimental structure

and conformational energy differences for individual molecules. The MM3 method has parameters for more atom types and addresses known problems with the MM2 method.

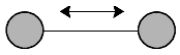
Fundamental Aspects of molecular mechanics

The molecular mechanics view of a molecule has spheres of different mass (atoms) connected together by a variety of springs (chemical bonds). If we can find the coordinates of all the atoms at the place where all the springs are at their equilibrium length, this should correspond to the lowest energy state of the molecule. Dynamic behavior of the molecule could also be calculated through application of the laws of classical mechanics.

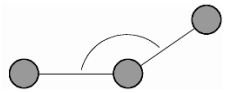
In real molecules, there are other forces present than just those between bonded atoms. There may be charges present that can repel or attract. Repulsions between nonbonded atoms that are close together in space might also occur. These forces may act to change bond angles or cause twisting around single bonds. To describe the energy of the system, we have to account for all of the different types of interactions that are applicable. The sum of the energy of all of these various components is the basis of a *force field*. A force field allows for calculation of all the forces on the system which in turn gives the energy of the system. In order to create a force field, we need a mathematical equation for each energy term as well as any required parameters (constants) for these equations The equations come from classical physics, and the parameters come from either experimental data, or from higher level quantum mechanics calculations.

Some of the energy terms that need to be taken into account are:

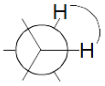
(1) Bond stretching



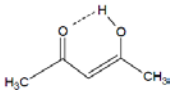
(2) Bond angle bending



(3) Dihedral angle rotation



(4) van der Waals forces

(5) Hydrogen bonding 

(6) Electrostatic interactions

Since molecular mechanics views chemical bonds as springs, an equation from physics called the harmonic oscillator approximationis used to describe this behavior:

$$E_{stretch} = \frac{k_s}{2}(l - l_0)^2$$

k_s = spring constant; l_0 = equilibrium bond length

Bond angle bending is treated with a similar equation:

$$E_\theta = \frac{k_\theta}{2}(\theta - \theta_0)^2$$

k_θ = spring force constant; θ_0 = equilibrium bond angle

Rotation about a single bond (torsion) changes the dihedral angle (Φ) and involves a sum of periodic functions. As the dihedral angle changes from 0□° to 360°, the energy profile will begin to repeat itself.

$$E_{torsion} = \frac{1}{2}V_1(1+\cos\phi)+\frac{1}{2}V_2(1+\cos 2\phi)+\frac{1}{2}V_3(1+\cos 3\phi)+\ldots?$$

V_n = dihedral force constant; n = periodicity; Φ = dihedral angle

Neutral atoms undergo a long range attractive van der Waals, or dispersion force. At shorter range, the electron clouds of atoms will begin to repel one another (Pauli repulsion). These two effects are modeled using the Lennard-Jones, or “6-12” potential:

$$E_{vdW} = \frac{A}{r^{12}} - \frac{B}{r^6}$$

A= repulsive term; B= attractive term

Hydrogen bonding is often handled in the van der Waals and electrostatic terms, but is sometimes placed in a separate term.

This “10-12” potential decays more rapidly with distance:

$$E_{HB} = \frac{C}{r^{12}} - \frac{D}{r^{10}}$$

Electrostatic interactions are based on Coulomb’s Law:

$$E_{electro} = \frac{q_a q_b}{\varepsilon_{ab} r_{ab}}$$

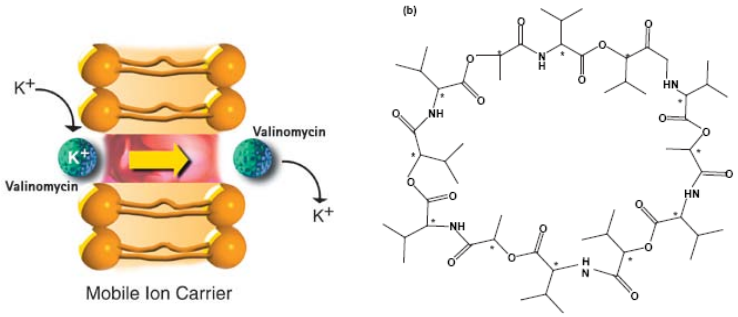
The steric energy, or total potential energy, of the system is given by a summation of all the energy terms:

$$E_{total} = E_{stretch} + E_{\theta} + E_{torsion} + E_{vdW} + E_{HB} + E_{electro}$$

The force field parameters in all of the above equations are typically determined for an example set of molecules, all of similar type. In order to achieve good results from a molecular mechanics calculation, the molecule of interest should be similar to those used in the parameterization procedure. Some force fields were developed for small organic molecules, while others apply better to proteins, or solid-state oxides, or inorganic molecules.

What is an ionophore?

Ionophores promote the transfer of ions from an aqueous medium into a hydrophobic phase.The inner part of an ionophore is made of polar groups forming a tetra- or octahedral geometry that fits and encloses the desired ion. Around this polar cage are hydrophobic groups that allow the solubilization of the charged ion-ionophore complex in apolar solvents or lipid membranes.Valinomycin is an example of a mobile ion carrier. It is a ring-shaped polymer that transports K^+ down its electrochemical gradient by picking up K^+ on one side of the membrane, diffusing across the bilayer, and releasing K^+ on the other side.



A natural compound: valinomycin (antibiotics)

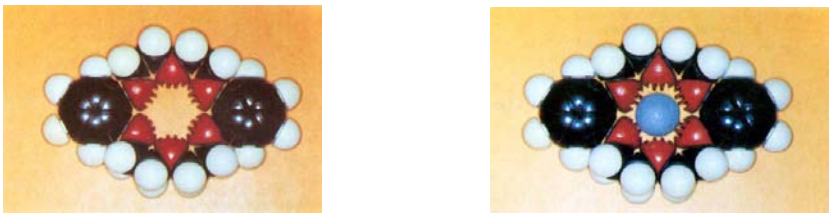
The ability to form a cage surrounded by polar groups is considered a necessary condition for ionophoric behavior.

Factors affecting ion binding and selectivity:

- Size match between cation and host cavity
- Electrostatic charge
- Solvent (polarity, H-bonds, co-ordination ability). Solvation energy is very important
- Host pre-organisation
- Enthalpy-entropy
- Counter-ion
- Chelate ring size

Crown ethers as ionophores

Ever since the award of the 1987 Nobel Prize to Cram, Lehn, and Pedersen “for their development and use of molecules with structure-specific interactions of high selectivity” studies of supramolecular sciences have become one of the major areas of scientific endeavor involving scientists from virtually all areas of sciences, including organic chemists, inorganic chemists, physical chemists, physicists, biochemists, and biologists.



Dibenzo-18-crown-6.

(a) free dibenzo-18-crown-6. (b) dibenzo-18-crown-6 captures K+ ion.

From "Crown Ethers & Cryptands" by G. Gokel, Royal Society of Chemistry, 1991

In this thesis molecular modeling of different ionophores (divided into five groups) is done with the help Quantum CAChe software to determine their selectivity for various metal ions. Crown ethers (one of the five groups of ionophores) are heterocyclic chemical compounds that consist of a ring containing several ether groups. Crown ethers strongly bind certain cations, forming complexes. The oxygen atoms are well situated to coordinate with a cation located at the interior of the ring, whereas the exterior of the ring is hydrophobic. The resulting cations often form salts that are soluble in nonpolar solvents, and for this reason crown ethers are useful in phase transfer catalysis (Pugia et al, 1986).

2,2-dipyridylamine (dpa) and its derivatives is another group on which study is done by Bianca et al, 2006. Pd(II) and Pt(II) complexes of such dpa derivatives have also been investigated as potential anticancer agents due to their structural similarity to cisplatin (Paul et al,1993; Puscasu et al, 2001; Rauterkus et al, 2003; C. Tu et al, 2003) The use of Ag(I) in a range of metal complex and supramolecular materials has received increasing attention, in part due to the coordination flexibility of this d^{10} ion and its well documented tendency to form strong complexes with nitrogen donor ligands (Steel and Sumby, 2002; Hiraoka et al, 2002; Dolomanov et al, 2004; Amoore 2005; Khlobystov, 2001**).** Further, the silver centres in such materials have frequently been associated with 'supramolecular' interactions (including silver–p interactions) (Munakata et al, 2000; Awaleh et al, 2005; Hanton et al, 2006; Wang et al, 2002) and in some instances give rise to unusual electronic and photophysical properties (Yeh et al, 2005; Dong et al, 2005).

Another group is 8-Hydroxyquinoline and its derivatives (Mittal et al, 2007) which is a unique class of complexing agents in which each of three legs, containing at least one donor atom (X,Yand Z), is connected to a bridgehead atom. The terminal groups may be hydrogens, alkyl groups, halogens, aromatic groups and other substitutents. Because of structural constraints, quadridentate tripodal ligands cannot coordinate in a planar fashion but tend to be well suited for tetrahedral coordination.

Literature Survey

There have been numerous theoretical studies of crown ethers that have provided new insights into crown cation interactions. These include ab initio (Hori et al, 1983; Ha,Y.L., 1992) semiempirical (Yamabe et al, 1979), and molecular mechanics (MM) (Hancock,1990; Hay et al,1993; Mazor et al 1990). In a seminal study, Wipff et al, (1985) attributed the preferential binding of 18-crown-6 (18C6) with K^+ over Na^+, in H_20, to the greater difference in hydration energies of the cations relative to their intrinisic complexation energies with 18C6. Indeed, it is possible to change the selectivity of 18C6 for the alkali metal cations by changing the dielectric constant of the solvent. Though their theoretical results indicated that 18C6 exhibited selectivity for Rb^+ over K^+ (contrary to experiment), Wipff et al. did demonstrate the high degree of conformational flexibility of 18C6 in interactions with the alkali metal cations. Recently, Glendening et al (1994) have utilized ab initio methods to compute binding enthalpies of 18C6 for the alkali metal cations, Li^+, Na^+, K^+, Rb^+ and Cs^+. Their study utilized large basic sets and results obtained at the second-order Moller-Plesset (MP2) perturbation level. Their calculations clearly show that solvation effects strongly influence cation selectivity. Their gas-phase calculations show 18C6 preferentially binds Li^+, not K^+, as found in aqueous environments.

18-crown-6 has its oxygens too far apart to form many optimum oxygen cation interactions with Li^+ or Na^+. Thus, it binds K^+ optimally because the solvation interactions Li^+ and Na^+ must give up to bind 18-crown-6 are not sufficiently compensated by strong ion-ionophore interactions

TABLE(II) – Atomic radii and cavity diameters of some common metal ion and crown ethers

Cation	Radius A°	Cation	Radius A°	Macrocyclic ring	Radii A°
Li^+	0.74	Mg^{2+}	0.72	15C5	0.86-0.92
Na^+	1.02	Ca^{2+}	1.00	18C6	1.34-1.43
K^+	1.38	Sr^{2+}	1.16		
Rb^+	1.49	Ba^{2+}	1.36		
Cs^+	1.70	Ag^+	1.15		

18C6 as a host and the potassium ion as a guest was chosen in view of the perfect fit between hole size (1.385 Å), and guest diameter (1.38 Å). Among monovalent cations, the selectivity order of 15C5 in methanol is $K^+ > Ag^+ > Na^+ > Cs^+$ as found by Izatt et al, (1980).

Other factors also dominate in determining cation selectivity. Some of these factors are cation solvation energies (which, in fact, explain the selectivity $K^+ > Na^+$), the formation of complexes of stoichiometry other than 1:1, and the solvation energy of the complex. Since these factors are often difficult to predict, the selectivity of a particular macrocyclic ligand among cations too large to enter its cavity is likewise difficult to predict.

The cavity size of 18C6 is large enough to allow entry of all cations studied except Rb^+ and Cs^+. The size of Rb^+ is only slightly larger than the upper boundary for the size of the ligand cavity of 18C6. The sizes of K^+ and Ba^{2+} match that of the ligand cavity very closely (Table II) and the selectivity of 18C6 for these two cations over others in their respective groups in the periodic table is well established. In proceeding through the series 15C5, 18C6, the cavity sizes of the ligands increase from being smaller than the size of Na^+ in the case of 15C5 to being as large as the largest cation studied.

Ab initio results were reported by Feller et al, 1994 that included a study of the nature of the complexes formed between 18C6 and different alkali and alkaline earth metal cations. It was concluded that the C_i conformation is more stable by 4.2, 4.4, and 5.4 kcal/mol than the D_{3d} conformation.

Al-Jallal et al(2005) did a conformational search for 18-crown-6 using the CONLEX method at the MM3 level. To have a more accurate energy order of the predicted conformations, the predicted conformations were geometry optimized at the HF/STO-3G level.

In an another study conducted by Grootenhuis and Kollman, (1989) on DB18C6, its complexes with alkali cations were energy minimized using AMBER**.**

For all molecular mechanics and dynamics calculations the AMBER package was used, in which the energy function is of the form:

$$E_{\text{total}} = \sum_{\text{bonds}} K_r (r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}} \right] + \sum_{\text{H-bonds}} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right]$$

Movement of one atom affects the atoms around it. E_{bonds} accounts for bond stretching where energy increases when a bond (spring) is pushed or pulled. E_{vdw} goes up when atoms are too close to each other, but no bond is formed.

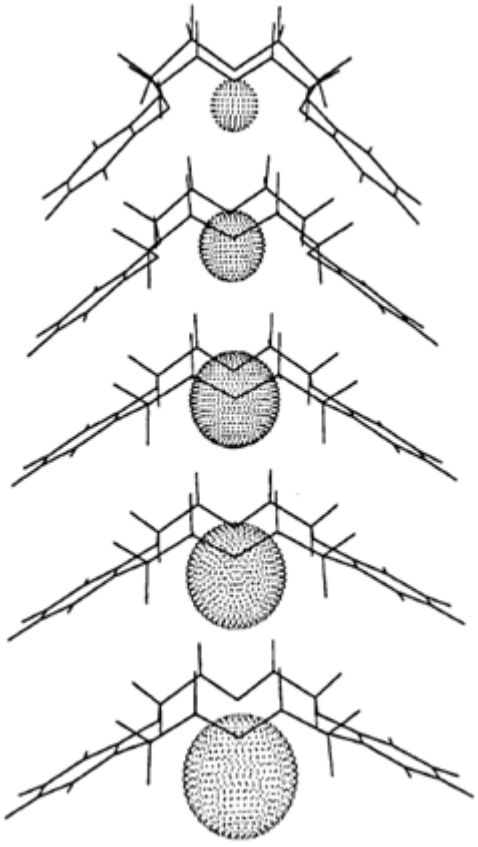


Fig. 1: Side view of the molecular mechanics minimized complexes of dibenzo-18-crown-6 with the alkalie cations. Top to bottom: the complexes with Li^+, Na^+, K^+, Rb^+ and Cs^+ ion

The results of the minimizations are given in Table III and in Figure 1. All complexes of the 18-membered macrocycle remained in approximately the same conformation as

observed in the X-ray structure; only the position of the cation relative to the crown ether changed as the size of the cation changed.

Table III. Interaction Energies (kcal /mol) Calculated by Grootenhuis and Kollman (1989) for ether-cation complexes with the help of AMBER

Cation	DB18C6
Li^+	-88.3
Na^+	-72.5
K^+	-62.4
Rb^+	-55.1
Cs^+	-47.0

For 15C5 crown ether a combination of classical force field molecular dynamics and electronic structure calculations were used by Hill and Feller(2000) to identify the low-lying, gas phase conformations of isolated 15-crown-5 and complexes it forms with a single alkali cation (Li^+, Na^+, K^+, Rb^+ and Cs^+). The computed binding enthalpies are compared with recent gas phase, collision-induced dissociation measurements. While agreement is reasonably good for sodium and potassium, it worsens for the larger cations, where theory and experiment differ by as much as 20 kcal/mol.

The formation of alkali-metal ion complexes with the crown ethers, 18-crown-6(18C6), benzo-18C6 and dibenzo-18C6 has been investigated by Wilson et al(1997). Theoretical studies of structural changes on complexation, binding energies and changes in electron distribution have been carried out using ab initio quantum theoretical methods and studied their interaction with potassium ion in various solvents (Islam et al, 1997). A complementary study of the NMR chemical shifts and coupling constants has also been used to obtain information on complexation and structural changes.

Objectives

Objective of this thesis is to determine selectivity of ionophore for particular cation, with the help of Quantum CAChe software. It further includes study of different parameters involved in determination of ionophore for particular cation like molecular mechanics (MM3), PM5(used for few ions like Na^+, K^+ etc.) in gaseous phase. The MM3 force field used in optimizing the structure of molecule includes and calculate energy. It also includes calculations of following parameters:

Bond stretch
Bond angle
Dihedral angle
Improper torsion
Torsion stretch
Bend Bend
Van der Waals
Electrostatics
Hydrogen bond

A molecule is considered as a collection of atoms held together by classical forces. These forces are described by potential energy functions of structural features like bond lengths, bond angles, torsional (dihedral) angles, etc.

The energy of a molecule is calculated as a sum of terms as given in equation:

$$E = E_{stretching} + E_{bending} + E_{torsion} + E_{vanderwaals} + E_{electrostatic} + E_{hydrogen\ bond} + \text{cross terms}$$

The first four terms are the energies due to deviations of bond lengths, bond angles, torsional angles and non bonded distances, respectively. $E_{electrostatic}$ gives the electrostatic repulsion or attraction between bond dipoles or partial atomic charges. More advanced force fields include cross terms such as stretch-bend, bend-bend etc. These terms are of importance for the accurate calculations of geometric properties of small rings (stretch-bend term) or for the calculation of vibrational frequencies (bend-bend term).

Experimental Work

Experimental work includes various steps like drawing of the structure of the ionophore, its optimization then it is complexed with a particular metal ion and finally optimization of the complex. Following steps are followed to obtain an optimized structure:

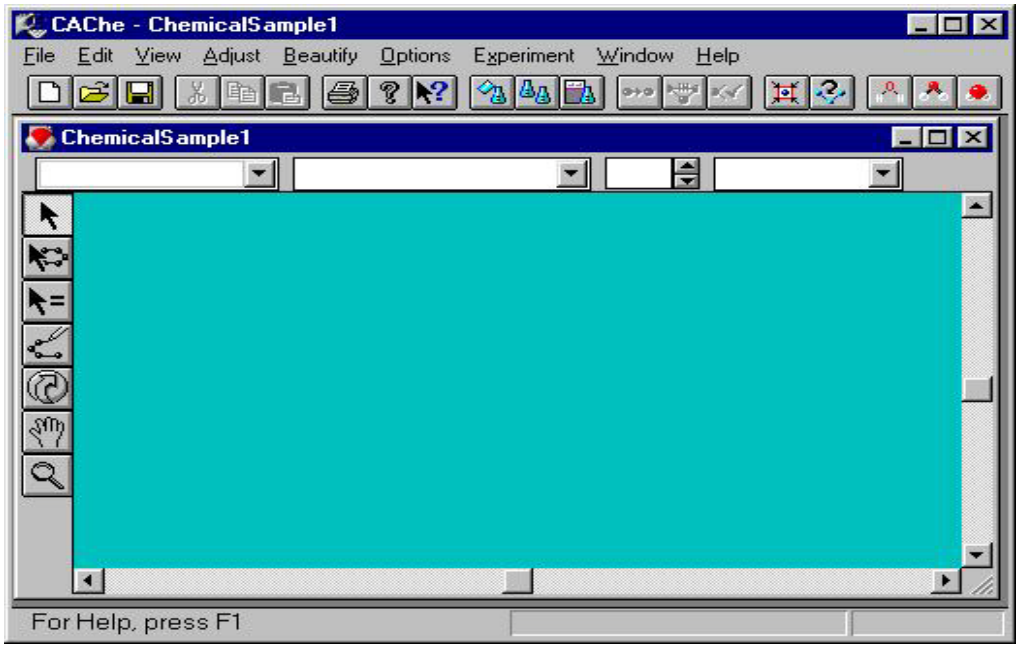
1. Structure of ionophore is either drawn in cache workspace or can be drawn in other software and then imported to cache. Its optimization is done.
2. Cation is added to the ionophore structure. After setting its configuration ,charge and type of bond, structure is beautified.
3. Save the structure and then optimization is done as per the steps shown below.

Steps to be followed for energy minimization

Energy minimization is a process in which bond distances and angles are adjusted incrementally to produce a lower energy structure.

To draw an atom

This is the main CAChe screen that will appear when you open the CAChe molecular modeling program.



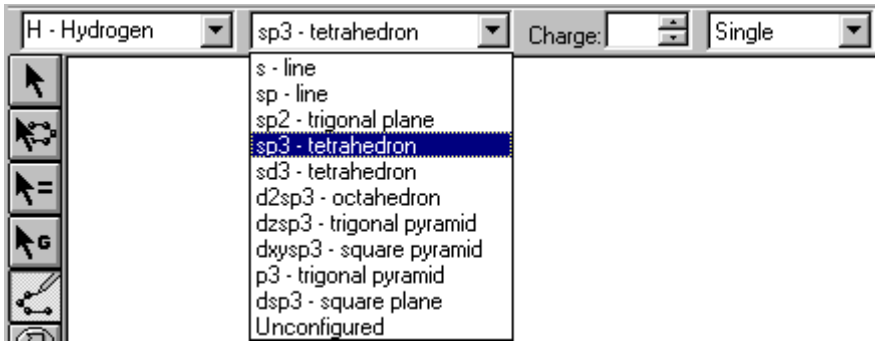
When the program opens it will always have the select arrow chosen. 

Now either we can draw the structure in this window directly or can draw the structure in other software like Chem Draw or ISIS draw and can copy paste in this window.

1. Select the arrow button in the Element Type box at the left of the style bar.

   A drop-down list of elements is displayed.

2. Choose an element type from the drop-down list to draw the element
3. Select the arrow button in the Hybridization box in the style bar.



4. Choose a hybridization from the drop-down list.

   The atom you are going to draw will possess hybridization of the chosen value.

5. Select the up or down arrow button in the Charge text box in the style bar until the positive or negative charge value you require is displayed

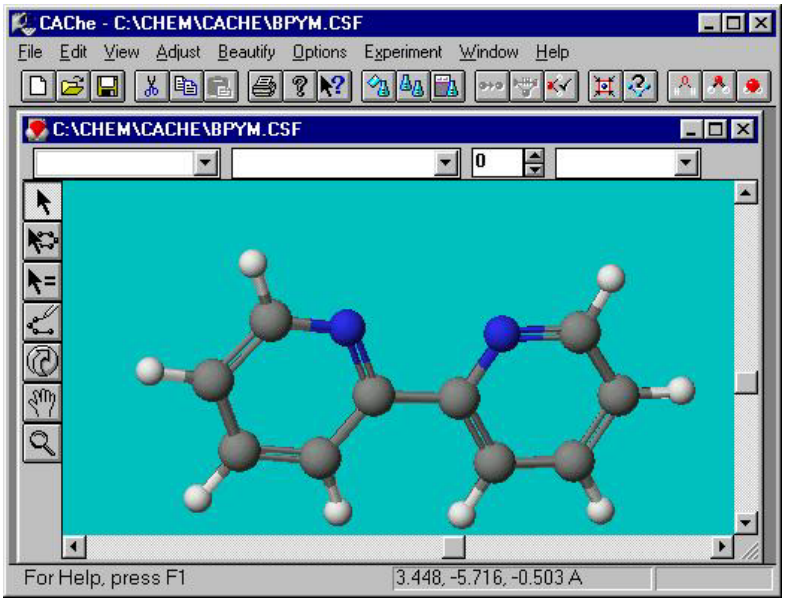
Completing the molecule

Complete the molecule in one of the following ways:

• continue to draw individual atoms, then join them by drawing bonds between each atom

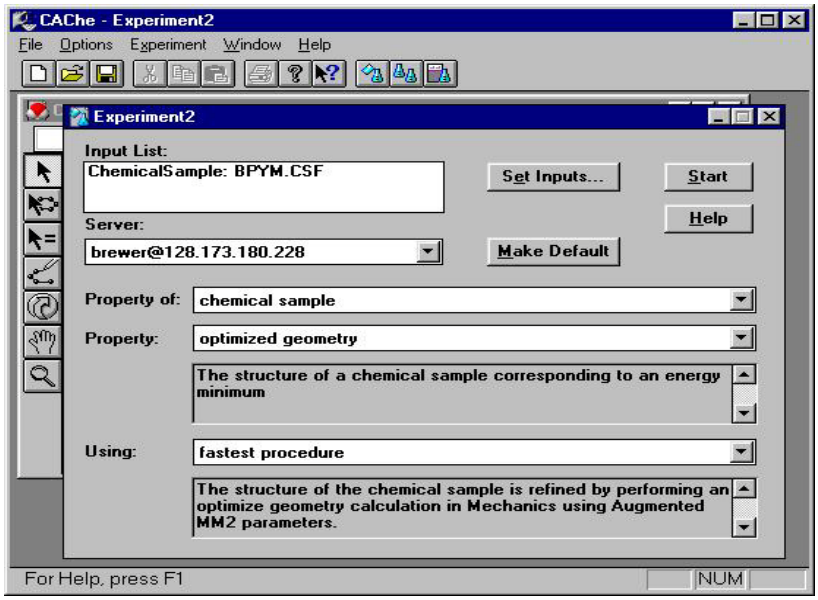
• continue to draw bonds with an attached atom.

Finish ring structures by completing the last bond you draw over the first atom that was drawn.



Now to set up a new experiment click on the *New Experiment* button. 

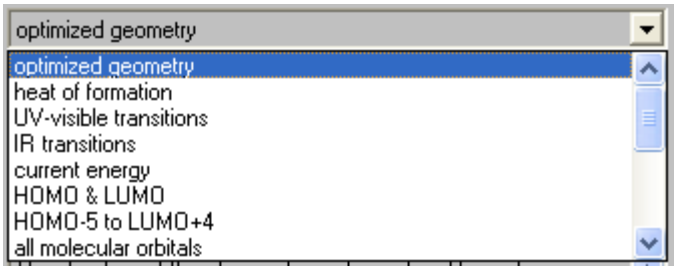
This is the dialog box that will appear after you have clicked on the *New Experiment* button.



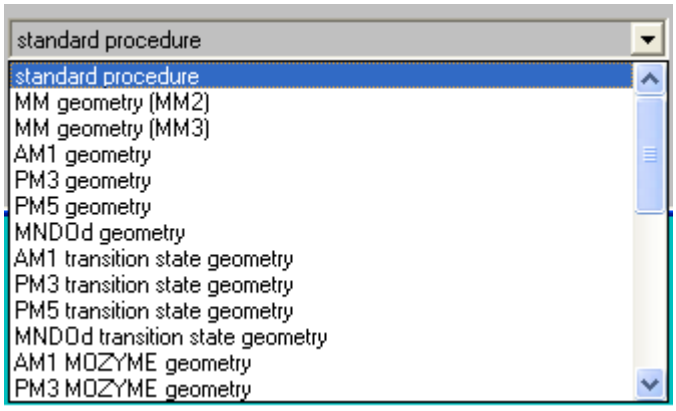
This *New Experiment* dialog box will appear, as shown, on top of your current chemical sample window. Below this is an *Input List*, this indicates that our experiment will be performed on the chemical sample in the "bpym.csf" file.

The next three dialog boxes; the *Property of*, *Property* and *Using* boxes; are the ones you use to select the type of experiment you would like to perform. It is important to select the *Property of* parameter first, then the *Property* parameter and finally the *Using* parameter since the items in the *Property* and *Using* boxes change as a function of the selection in the *Property of* dialog box.

To perform an energy minimization on the entire chemical sample, then the *Property of* box should be displaying "chemical sample". Now we need to input the *Property* we would like for the CAChe system to calculate. To do this click on the *Down Arrow* on the *Property* dialog box. This should bring up a list of properties that you can calculate. This list allows you to determine what chemical property you are interested in calculating We want to calculate an optimized geometry, so click on "optimized geometry".

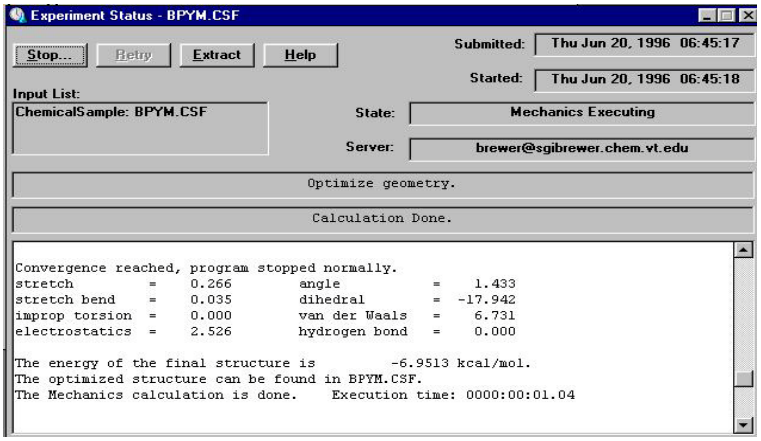


Next is to set the parameter in the *Using* box. This box determines which calculational method is used to calculate the property listed in the *Property* box. Click on the *Down Arrow* on the *Using* box and you will see a list of selections to calculate a molecular mechanics energy minimized structure. This is shown in the list as "MM geometry".



Click on this option to tell the server to use molecular mechanics to calculate your "optimized geometry".

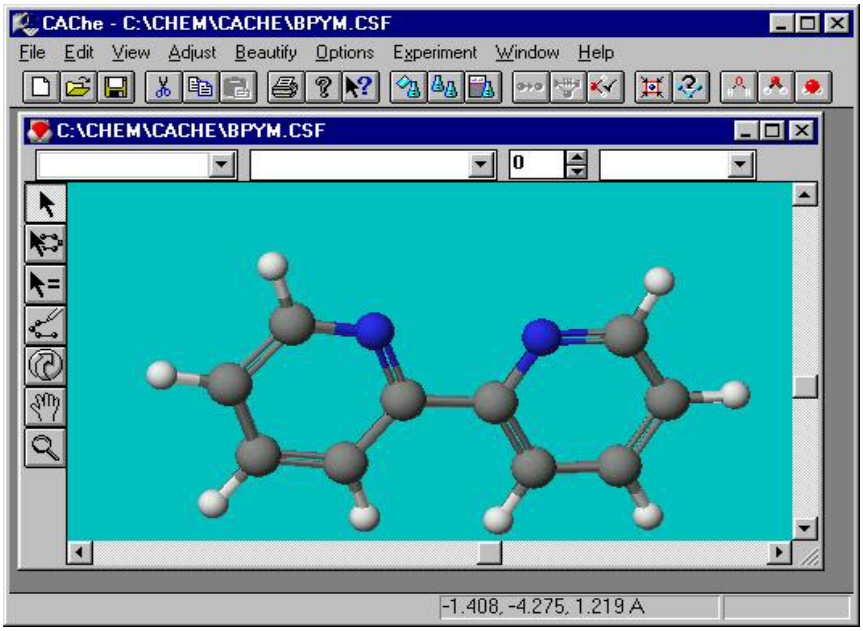
Now we are ready to ask the server to do our calculation and this can be done by clicking on the Start button. This is the *Experiment Status* box that appears after starting the molecular mechanics energy minimization calculation.



This calculation is very fast and may be finished within a few seconds. This *Experiment Status* box has a number of options as well as some very useful information.

The *Stop* button at the top left allows you to stop your calculation In the upper right corner are two boxes showing: *Submitted*, the time you submitted your calculation; and *Started*, the time your calculation started to execute.

Below these boxes is the *State* box that gives very useful information on the exact status of your calculation. In this *State* box it indicates that "Mechanics (is) Executing". This means that your mechanics calculation is currently being executed by the server. Other important *State* entries include: "Pending", which means you are waiting your turn for the server to perform your calculation; and "Done", which means your calculation is finished and the output has been transferred to your computer. You need to wait until the *State* box indicates that the job is "Done".



This image will look very similar to the bpy chemical sample you created when you first constructed this ligand. This is a result of the fact that the CAChe *Beautify* command works very well on small organic compounds. A more pronounced differences is observed with larger organic compounds and with inorganic transition metal complexes.

Once an energy minimized structure is generated view bond distances and bond angles in the structure can be viewed. The most convenient way to do this is to use the *Adjust* drag down menu and the *Define Geometry Label* option.

To view a bond distance, use the select arrow to select one atom and then hold down the *Shift* key and select a second, connected atom. Now use the *Adjust* drag down menu and click on *Define Geometry Label*

Parameter used during this project for optimization of ionophore-metal ion complex

1. Parameter used for energy minimization is standard (it includes MM3)
2. Interaction between metal and donor atom is weak except in mdpa, pdpa, diypy molecules
3. For some ions (Na^+, K^+) PM5 parameter is used for energy minization because for them data is not available in MM3 parameter.

Results and Discussion

Computational studies were done to find energy content values of some ionophore molecules with a number of alkali, alkaline and transition metal ions.

The ionophore molecules can be divided in five groups:

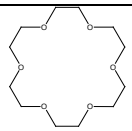
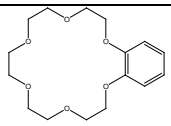
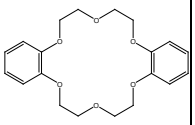
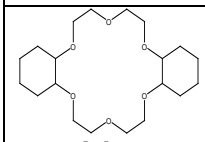
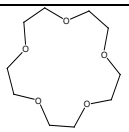
1) Crown ethers
2) Thiasulphide derivatives
3) 8-Hydroxyquinoline derivatives
4) Cyclic and open chain amides
5) Dipyridyl amine derivatives

Energy minimization studies on each of the ionophore molecules complexed with the selected metal ion was carried out and reported below.

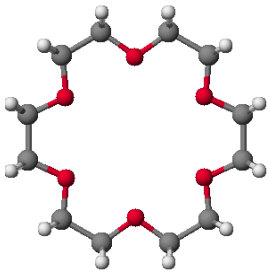
Group 1 : **Crown Ethers**

Energy minimization studies were carried out using CAChe 6.01 software for some common crown ether molecules (Table 1) for complexation with some alkali, alkaline earth and transition metal ions. Results indicate that 18C6 preferably binds with potassium ions. Similarly B18C6, DB18C6, Dicyclohexyl18C6 binds preferably with potassium ion in comparison to other alkali, alkaline earth, transition and some p-group elements as shown in the Table 1. Reason for this behavior can be a suitable cavity size of the crown ethers for K^+ ion (ionic radii 1.38A$^\circ$). Besides this, hard and soft acid base concept also supports the interaction of soft oxygen atom and soft K^+ ion.

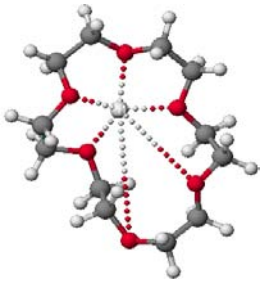
Table 1: Optimized energy (in kcal/mol) of complexes of different crown ethers with some metal ions

Crown Ethers	Energy in Kcal/mol (with different metal ions)									
	Li^{+}	Na^{+}	K^{+}	Ag^{+}	Mg^{+2}	Ca^{+2}	Cu^{+2}	Zn^{+2}	Pb^{+2}	Hg^{+2}
 18C6	336.2	273.1	**242.1**	308.8	429.5	377.4	486.4	422.5	385.5	375.5
 B18C6	301.0	231.3	**195.9**	271.3	367.0	310.0	428.6	400.0	351.0	342.7
 DB18C6	161.3	191.7	**151.1**	169.0	307.8	245.3	374.1	257.9	250.1	239.8
 Dicyclohexano-18C6	295.0	272.2	**239.7**	293.6	416.3	382.2	465.3	440.2	422.8	413.5
 15C5	223.0	**193.1**	201.5	229.7	333.8	316.7	353.0	347.2	356.6	348.7

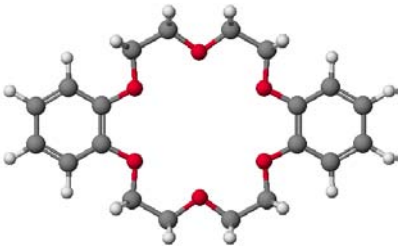
15C5 shows lower energy for complex with sodium ion (193.1 kcal/mol) where as for potassium the values is very close to it i.e., 201.5kcal/mol. These crown ethers show much higher energy of complexes with metal ions: Ag^{+} (1.26A$^{\circ}$), Mg^{+2}(0.65 A$^{\circ}$), Ca^{+2}(0.99 A$^{\circ}$), Cu^{+2}(0.72 A$^{\circ}$), Zn^{+2}(0.74A$^{\circ}$), Pb^{+2}(1.20 A$^{\circ}$), Hg^{+2}(1.10 A$^{\circ}$), respectively, probably because of the mismatch(either too small or too big size of metal ions with respect to cavity size of crown ethers) of ionic radii of these metal ions and the crown ethers.



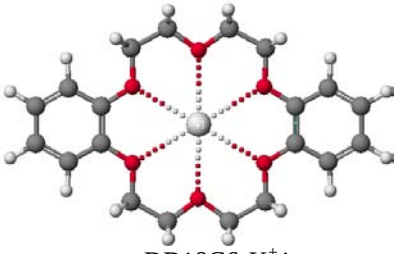
18C6



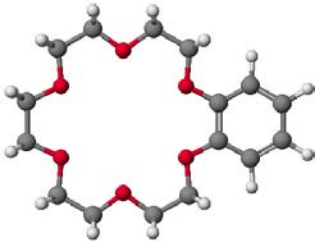
18C6-K^+ ion



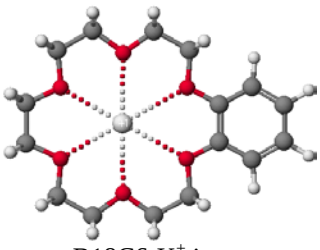
DB18C6



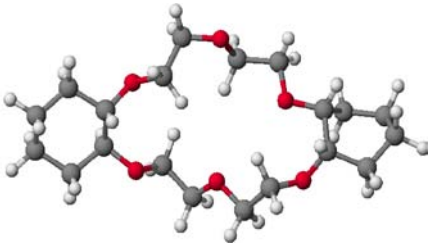
DB18C6-K^+ ion



B18C6

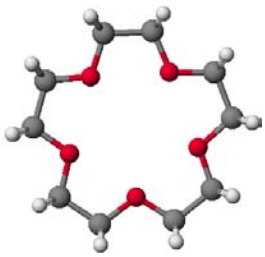


B18C6-K^+ ion



Dicyclohexano 18C6

Dicyclohexano 18C6- K^+ ion



15C5

15C5 – Na^+ ion

Fig. 1: Shapes of crown ethers and energy optimized structures with metal ions.

The stability order of these complexes can be shown as below.

For 18C6
$K^+ > Na^+ > Li^+ > Ag^+ > Hg^{+2} > Pb^{+2} > Zn^{+2} > Fe^{+2} > Cu^{+2}$

For DB18C6
$K^+ > Li^+ > Na^+ > Ag^+ > Hg^{+2} > Pb^{+2} > Zn^{+2} > Fe^{+2} > Cu^{+2}$

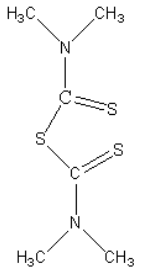
For 15C5
$Na^+ > K^+ > Li^+ > Ag^+ > Zn^{+2} > Hg^{+2} > Cu^{+2} > Pb^{+2}$

For Dicyclohexano-18C6
$K^+ > Na^+ > Ag^+ > Li^+ > Hg^{+2} > Pb^{+2} > Zn^{+2} > Cu^{+2}$

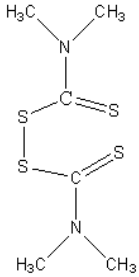
For Benzo18C6
$K^+ > Na^+ > Ag^+ > Li^+ > Hg^{+2} > Pb^{+2} > Zn^{+2} > Cu^+$

Group 2: Thiasulphide derivatives

These molecules are sulphur based podands tetramethylthiamonosulphide(TMTMS) and tetramethylthia disulphide (TMTDS) and are known to behave as ionophores to complex with alkali metal ions. Interaction with other metal ions have also been studied and energy values of metal complex with these ionophores are reported in Table 2.



TMTMS (I)



TMTDS(II)

Both molecules indicate preference for complexation with Na^+ ions as their respective energy values are the lowest. Energy values with Ag^+ ions also are also low because of the soft nature of S atom and also that of Ag^+ ions. As seen in Fig. 2 the concept of cavity size doesnot seem to hold good, as no cavity is being formed by the ionophore. Ca^{2+} ions on the other hand, even being very similar to Na^+ ions in size, show high energy because the hard soft acid base concept does not hold good. In this case complexation with Fe(III) ions is not favoured preferably because of large ionic radius of this d^5 system.

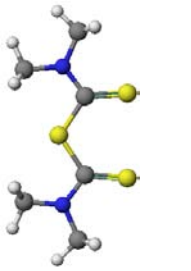
Table 2: Energy (kcal/mol) of the optimized confirmations of the molecules with different ions (from Quantum CAChe)

Metal ions	Energy (I) In kcal/mol	Energy (II) In kcal/mol
Na^{+}	**16.8**	**31.5**
Ca^{2+}	30.5	42.9
Fe^{3+}	55.4	63.3
Ni^{2+}	38.0	48.7
Cu^{2+}	25.0	55.1
Zn^{2+}	36.2	46.8
Hg^{2+}	32.6	44.4
Pb^{2+}	33.6	44.7
Ag^{+}	17.8	31.9
Al^{3+}	55.1	62.5

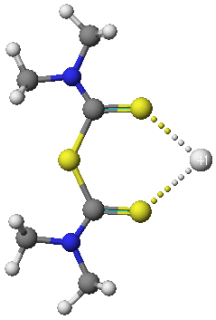
Stability order of the two complexes is as given below:

Structure I: $Na^{+}>Ag^{+}>Cu^{2+}>Ca^{2+}>Hg^{2+}>Pb^{2+}>Zn^{2+}$

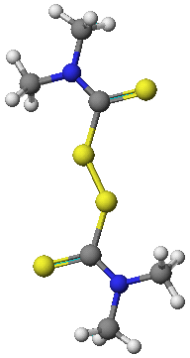
Structure II: $Na^{+}>\sim Ag^{+}>Pb^{2+}>\sim Hg^{2+}>Zn^{2+}\sim Cu^{2+}$



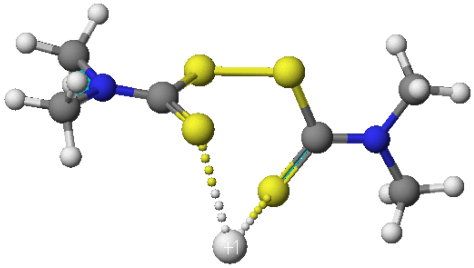
I



I with Na^{+} ion



II

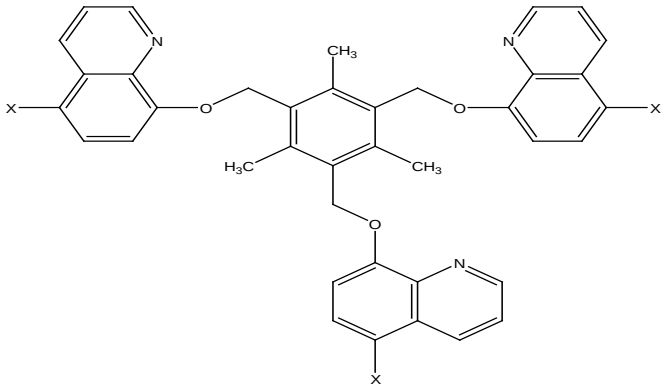


II with Na^{+} ion

Fig. 2 : Energy optimized structures of ionophore I and II and their complexes with sodium ion

Group 3: 8-Hydroxyquinoline derivatives

Group 3 includes tripodal ionophores with three substituents at 2, 4 and 6 positions of the benzene ring. Substitunts are derivatives of 8HQ with –H, -Cl, $-NO_2$ and CH_3 groups at para position to the ether linkage.



I

Quantum CAChe calculations indicate that the ionophore with X= H forms lowest energy complex with Hg^{2+} ions. For X= Cl, the molecules tend to form complex preferably with Ag^{+} ions where as, with X = NO_2, the ionophore tends to minimize energy with Mg^{2+} and Fe^{2+}, almost with equal stability. When methyl group is taken as a substituent, the tripodal complex shows minimum energy again with Ag^{+} ions.

Table 3: Energy (kcal/mol) of the optimized confirmations of the molecules with different ions

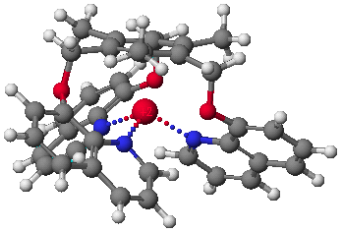
Ionophores	**Energy in kcal/mol**							
	Mg^{2+}	**Al^{3+}**	**Ag^{+}**	**Zn^{2+}**	**Pb^{2+}**	**Cu^{2+}**	**Fe^{2+}**	**Hg^{2+}**
X = H	234.5	350.9	230.2	292.2	291.0	562.8	592.7	**227.2**
X = Cl	220.8	305.5	**175.5**	238.3	244.7	244.1	233.0	239.0
X= NO_2	**38.3**	102.4	82.6	57 .4	67.7	300.4	39.1	64.1
X=CH_3	218.3	300.5	**180.1**	238.4	246.1	240.2	232.7	235.5

These different behaviours are due to the changing basicity of donor nitrogen atoms of 8HQ group which are in conjugation with the substituent. In the complexed structure of the molecule with Hg^{2+} ions, we can see very clearly that Hg^{2+} is coordinated by N atoms of 8HQ groups, while oxygen atoms of ether linkage remain at a distance and do

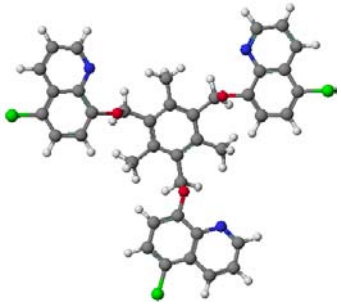
not participate in the complex formation. Therefore, the energy minimization is limited to the interaction of Hg^{2+} with nitrogen atoms.

It can be observed from Table 3, that the ionophore shows different energy values when H is substituted with -Cl, $-NO_2$ or $–CH_3$ group. For each metal ion energy values decrease when H is replaced with chlorine except for Hg^{2+} ion, when there is a marginal increase. Substitution of H with nitro results in a substantial decrease in energy of the complex for all the metal ions, for example, 234.5 kcal/mol decreases to 38.3 kcal/mol for complexation with Mg^{2+} ions. This clearly indicates that the effect of nitro group as a substituent increases stablisation of the complex. This inference is difficult to be explained by electron withdrawing nature of the nitro group, which acts as a coordinating site and result in weak interactions with the acidic metal ion. Substitution of H with methyl group result in a trend very similar to that of chloro substituent. This behavior is yet to be explained . Another hypothesis can be that the lone pairs on chloro substituent are behaving as base and its probable interaction with metal more than compensates for its electronegative effect on nitrogen of the adjacent ring. Therefore instead of an expected increase in energy from unsubstituted ionophore there is an actual lowering of energy.

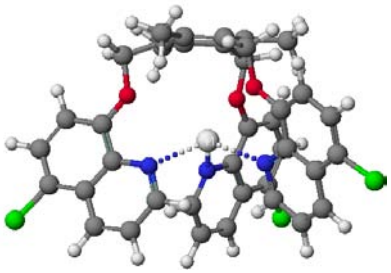
X=H



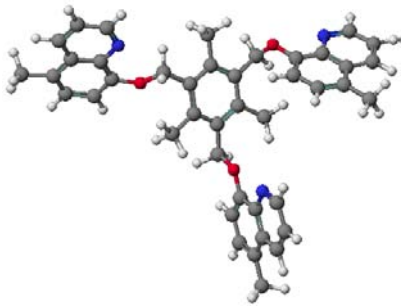
with Hg^{2+} ion



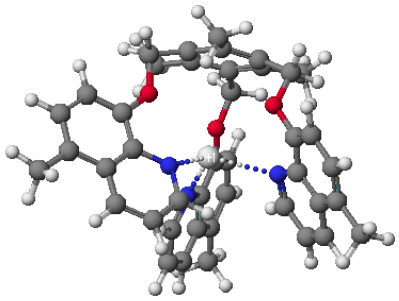
X=Cl



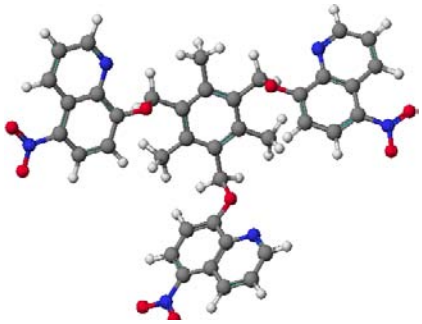
with Ag^{+} ion



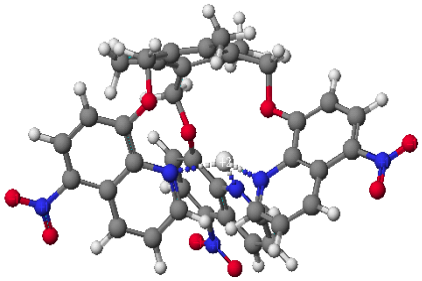
X = CH_3



with Ag^+ ion



X= NO_2

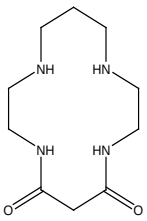


with Mg^{2+} ion

Fig 3:Complex structures of metal-ionophore complex after optimization.

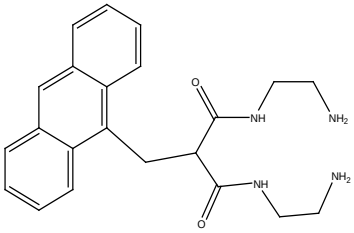
Group 4: Cyclic and open chain amides

Group 4 molecules contain amide groups with amine attached to para position. Molecule 1 is cyclic while molecule II is an open chain compound. Energies of optimized structure of these two molecules with a number of metal ions is shown in Table 4.



1,4,8,11 tetraazacyclotetradecane-5,7-dione

III

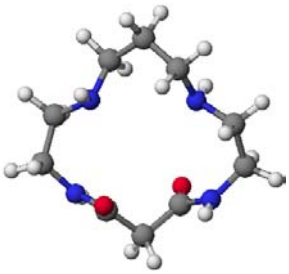


N,N'-bis(2-aminoethyl)-9-anthrylmethylmalonamide

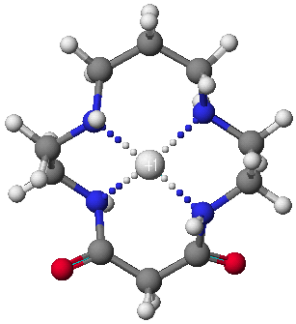
IV

Table 4: Energy values of optimised structures of the molecules III and IV with different metal ions

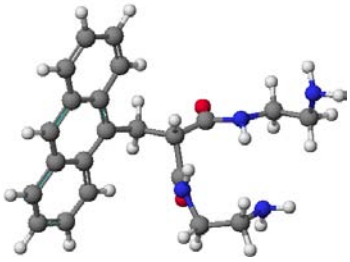
Metal ion	Energy in kcal/mol III	Energy in kcal/mol IV
Ag^{+}	**230.8**	**107.2**
Pb^{2+}	362.6	286.8
Hg^{2+}	352.0	397.9
Zn^{2+}	366.7	296.5
Cd^{2+}	347.4	275.5
Cu^{2+}	384.6	307.3
Ni^{2+}	352.4	284.5
Co^{2+}	351.0	295.5
Fe^{3+}	471.6	415.5



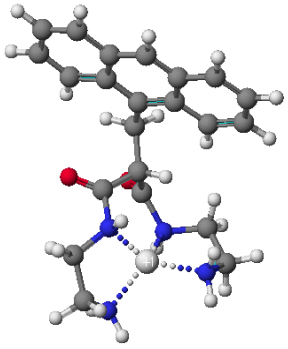
Dioxocyclam



Dioxocyclam – Ag^{+} complex



N,N'-bis(2-aminoethyl)-9-anthrylmethylmalonamide



N,N'-bis(2-aminoethyl)-9-anthrylmethylmalonamide – Ag^{+}

Fig. 4 structures of ionophore-metal ion complexes optimized with CAChe

Both molecule III and IV show highest energy content for Fe^{3+}, while it shows least value for Ag^{+} ions. Other metal ions show different energies with both molecules III and IV. In general, the energy content of cyclic ionophore with all the metal ions lie higher than

with those of open chain molecules, indicating that the open chain ionophores accommodates metal ions better than that of the closed ring ionophores. CAChe structures of the uncomplexed and complexed ionophores are shown in Figures III and IV. Orders of stability for structure III and IV with different metal ions are shown below. These type of molecules are recommended safely as ionophores in potentiometric chemical sensors for Ag^+ ions.

Stability order for structure III

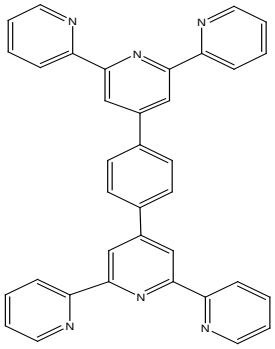
$Ag^+ > Cd^{+2} > Co^{+2} > Hg^{+2} \sim Ni^{+2} > Pb^{+2} > Zn^{+2} > Cu^{+2}$

For structure IV

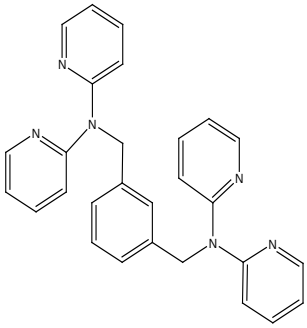
$Ag^+ > Cd^{+2} > Ni^{+2} > Pb^{+2} > Co^{+2} > Hg^{+2} > Zn^{+2} > Cu^{+2}$

Group 5: Dipyridyl amine derivatives

These compounds are again nitrogen containing compounds. These pyridine based compounds are complexed with four metal ions i.e., silver, lead, mercury and zinc and their energy values are calculated by using MM3 calculations on CAChe software.

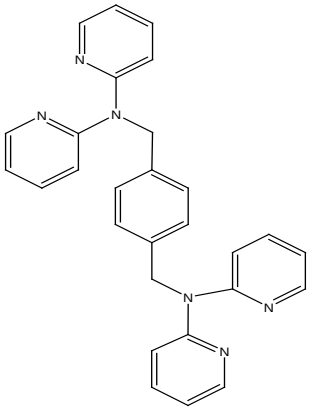


V
Ditpy

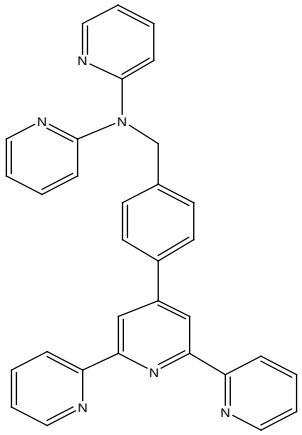


VI
mdpa

V : 4-(4-(2,6-di(pyridine-2-yl)pyridine-4-yl)phenyl)-2,6-di(pyridine-2-yl)pyridine
VI: N-(3-((dipyridin-2-ylamino)methyl)benzyl)-N-(pyridine-2-yl)pyridine-2-amine



VII
pdpa



VIII
tpydpa

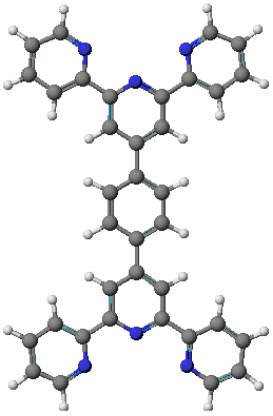
VII: N-(4-((dipyridin-2-ylamino)methyl)benzyl)-N-(pyridine-2-yl)pyridine-2-amine
VIII: N-(4-(2,6-di(pyridine-2-yl)pyridine-4-yl)benzyl-N-(pyridine-2-yl)pyridine-2-amine

Table 5: Energy(kcal/mol) of complex of structure V, VI, VII and VIII with metal ions complexing in 1:1(L:M) and 1:2(L:M) ratio

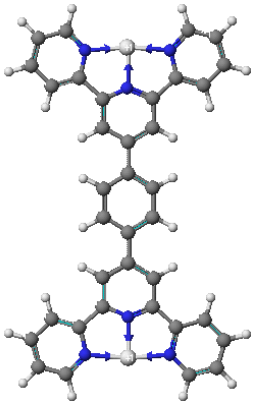
Metal ions	**Energy in kcal/mol(Coordinate bond)**							
	V		**VI**		**VII**		**VIII**	
	1:1	1:2	1:1	1:2	1:1	1:2	1:1	1:2
Ag^{+}	15670.9	285.6	165.9	**601.4**	675.8	**597.4**	441.4	**236.9**
Pb^{2+}	15170.4	**335.9**	442.7	781.4	**131.9**	776.7	244.2	544.9
Hg^{2+}	16509.4	383.3	183.7	709.8	187.4	689.5	291.8	538.7
Zn^{2+}	17169.7	321.8	**156.3**	656.2	164.7	650.9	**216.0**	481.2

Results as given in Table 5 indicate that molecule V forms 1:2 complex with Ag^{+} ions. The energy of 1:1 complex is extremely high probably due to the rigidity of structure of the compound which does not allow a molecule to flip so that nitrogen environment converges onto one metal ion. These calculations were verified experimentally as well, where stability constants for 1:2 was the highest (for VI- 5.71, for VII- 5.20 and for VIII- 13.28). For molecules VI, VII and VIII. 1:1 stiochiometry is preferred for complexation with mercury, lead and zinc ions, respectively. Amongst these 3 metal ions, the stablisation are almost to the same extent, with molecules VI, VII and VIII. For molecule VI mercury 183.7 kcal/mol against 709.8 kcal/mol; lead 131.9 kcal/mol in comparison to 776.7 kcal/mol for molecule VII, zinc with molecule VII 216.0 kcal/mol against 481.2

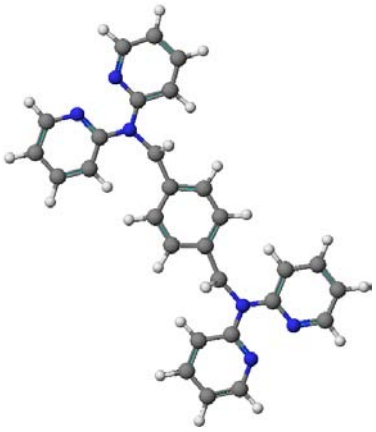
kcal/mol. Hence it can be seen very clearly from the following Figure and also from Table 5 that stereochemistry plays a very important role in the complexation behavior of the ionophore with the metal ions.



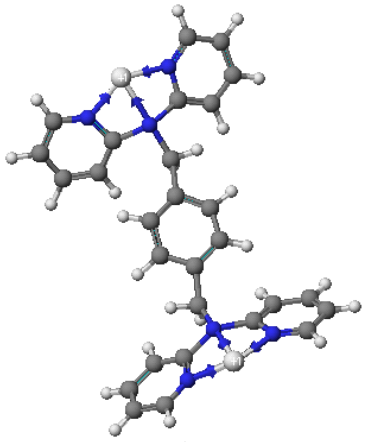
ditpy



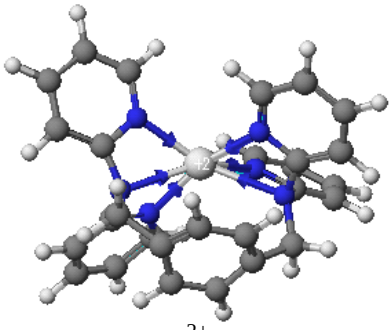
ditpy-Ag+



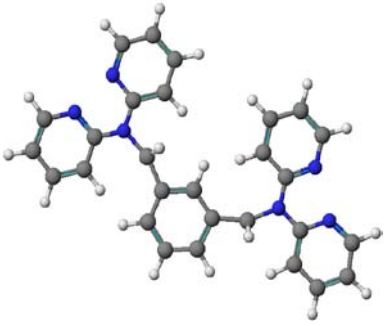
pdpa



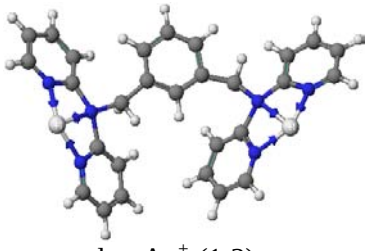
pdpa- Ag^{+} (1:2)



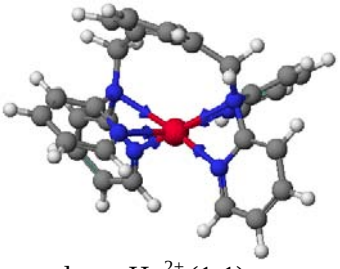
pdpa –Pb^{2+} (1:1)



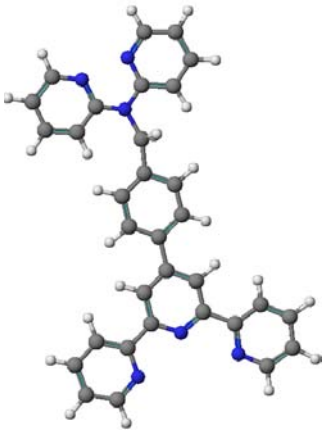
mdpa



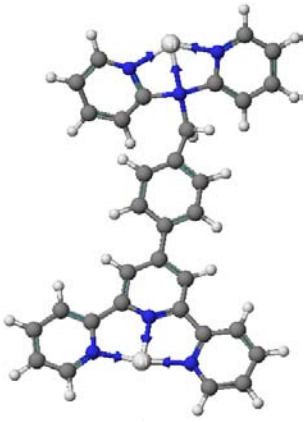
mdpa-Ag^{+} (1:2)



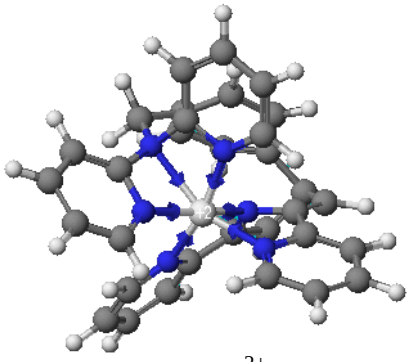
mdpa – Hg^{2+} (1:1)



tpydpa



tpydpa- Ag^{+} ion(1:2)



tpydpa- Zn^{2+} (1:1)

Conclusions

Computer simulations have been carried out for various groups of ionophores and their derivatives complexed with alkali, alkaline earth and transition metal ions, with the help of Quantum CAChe. Optimized energy values of the complexes formed by these ionophores with various metal ions shows their selectivity for a particular metal ion, like 18C6 is selective for K^{+} ion, 15C5 for Na^{+}. Pyridine amine derivatives form 2:1 complexes with silver ion and 1:1 complexes with other ions. Both dioxocyclam and N,N'-bis(2-aminoethyl)-9-anthrylmethylmalonamide, form stable complexes with silver ions and 8-HQ derivatives on the basis of substituents, form stable complexes with different ions. MM3 parameter of CAChe was used to calculate energy of optimized structure of complexes. Thus, molecular modeling with the help Quantum CAChe can be helpful in determining the selectivity of various ionophores for particular metal ions.

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