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A CLFSE/MM study on the role of ligand bite-angle in Cu(II)-catalyzed Diels-Alder reactions

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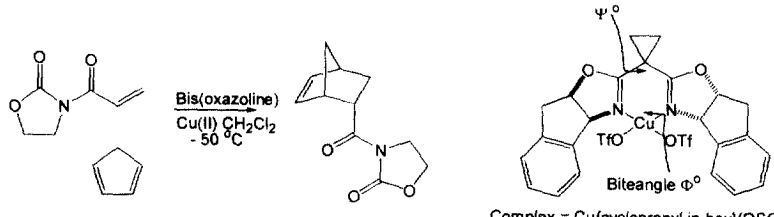
Abstract: A single force-field has been developed for modeling bis(oxazoline) and pyridine-bis(oxazoline) copper(II)-complexes. Using this force field the role of ligand bite–angle on the enantioselectivity of Cu(II)-catalyzed Diels-Alder was confirmed and for the first time, a direct comparison of the role of C-4 oxazoline substituents was achieved.

In a series of publications, the Evans group has demonstrated that bis(oxazoline) ['box'] and pyridine-bis(oxazoline) ['pybox'] systems are some of the most generally applicable ligands in asymmetric catalysis.[1] We have investigated the role of ligand conformation in Cu(II)-catalyzed two-point binding asymmetric Diels-Alder reactions (Scheme 1) using a conformational toolbox of oxazoline ligands.[2a] Highly enantioselective Diels-Alder reactions can be achieved with the correct choice of conformational constraints. In particular the ligand bite-angle plays an important role on the enantioselectivity and was correlated with the magnitude of the angle of the uncomplexed ligand.[2b] The critical shortfall was that the bite angle could not be correlated directly and an accurate description of the Cu(II)-complex could not be reproduced. Direct observation of the geometry and structural information for all these bis(oxazoline)-copper(II) complexes is not practical and inevitably the understanding of the selectivity was derived from inspection of molecular models or from simple qualitative calculations with 'user imposed' geometry.



Complex = Cu{cyclopropyl in-box}$(OSO_2CF_3)_2$

Scheme 1

Molecular Mechanics (MM) is a popular method for modeling molecular structure and conformational energies and,[3] given the complexity of the ligands, is the method of choice here. Well parameterized forcefields are available for treating organic problems by MM. However, extension of MM to inorganic chemistry and coordination compounds presents greater challenges. We have developed the Cellular Ligand Field Stabilization Energy/Molecular Mechanics (CLFSE/MM) approach that enables the electronic effects in open shell Werner complexes to be calculated. Copper(II) is probably the hardest metal for conventional MM. Of special note are the distorted non-cubic geometries displayed by d^9 Cu(II)-complexes and six coordinate Cu(II) species which are almost always tetragonally distorted. The CLSFE/MM is the first general empirical method for calculating Cu(II) structures handling any coordination number and geometry. The correct structures are automatically generated without resort to external constraints. The Jahn-Teller effect is implicit in the CLFSE and as such, requires no external constraints to be placed on the system. A full account of the CLFSE/MM implementation and the extension to potentially π-donating ligands have been published [4a] – a brief outline is given in reference 5. We have recently extended the CLFSE term to imines, pyridines, and imidazoles as prototypical π-bonding ligands.[4b]

In this paper we describe the development of a single unified force field capable of modeling Cu(II)-box and Cu(II)-pybox complexes. For the present study the aqua complexes were used as models for the Cu(II)box(imide) structures since Density Functional Theory (DFT) calculations of the Cu(II)-(imide)(box) complex gave similar geometries to the aqua complexes (as opposed to the chloro complexes). Further extensions to the imide complexes together with the aldehydes, glyoxylates and pyruvate esters will be reported in due course. One important feature is the ability to calculate the transition state structure of the desired reaction and this in approach that we are actively pursuing.

The six copper(II) complexes used for this study can be subdivided into two classes — box ligands and pybox ligands that contain a third potentially donating π-pyridine. Our goal was to develop a single unified FF capable of modeling all six structures. The structures of the monomeric complexes are shown in Scheme 2 (**X** represents the crystal structure and **C**

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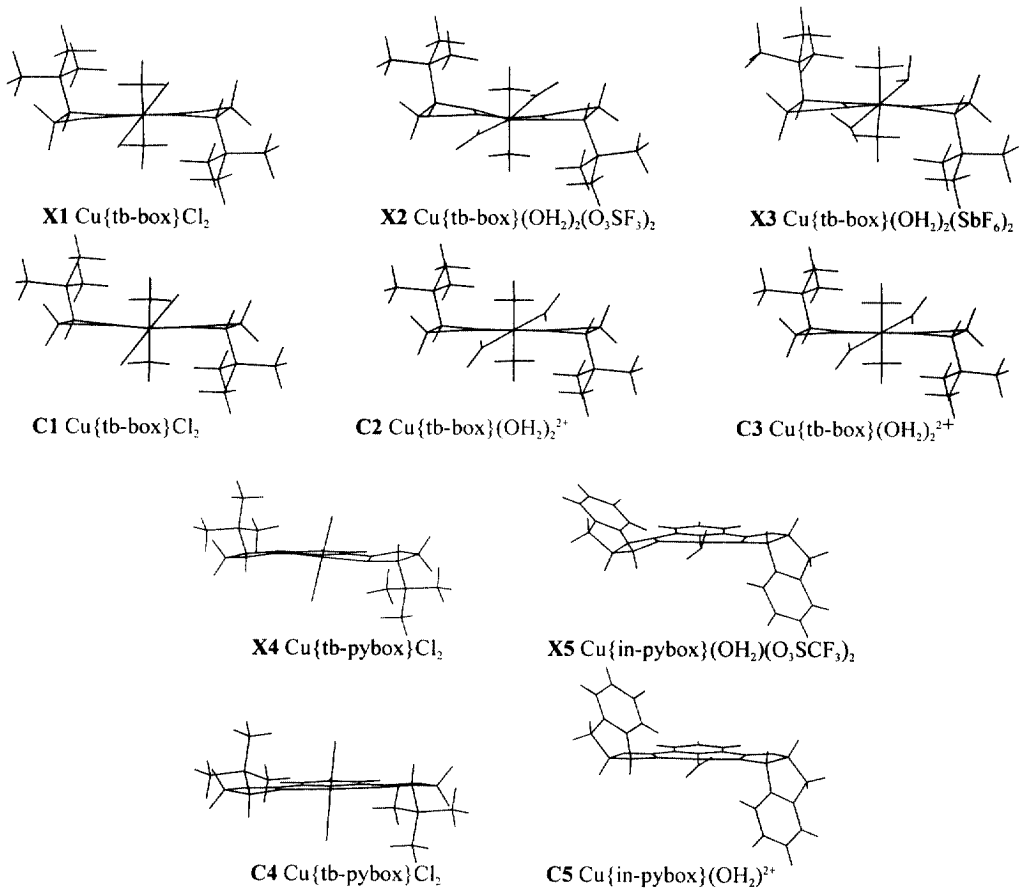
represents the calculated structure), the sixth structure Cu{ph-pybox}$_2$ $(O_3SCF_3)_2$ **X6** is not shown. As described previously,[4a] there are three ways of overcoming the inherent tendency of the CLFSE to enforce planar coordination in [CuL_4] species: (i) very large e_π values, (ii) very large van der Waals repulsion terms or (iii) ligand-ligand electrostatic interactions. The latter is certainly the most appealing, especially as we had already anticipated the need for electrostatics. Guided by the results for other imine systems, FF parameters for both Cu{tb-box}Cl_2 and [Cu{tb-box}$(H_2O)_2$ were developed. The initial FF, which included M-L and L-L electrostatic interactions was augmented and modified to accommodate the pybox systems as well. A reasonable set of FF parameters was obtained capable of reproducing the crystal structures with acceptable accuracy (Table 1 - 3). The FF reported for Cu(II)-imine systems[4b] was extended and slightly modified to accommodate the additional atoms types required. The most significant change is for the Cu-N-C angle bend force constant describing the metal-oxazoline bond. The value had to be decreased significantly to allow for the very different angles for box and pybox systems. This change does not materially affect the geometries of the imine structures reported previously.



Scheme 2

Overall, *the agreement between theory and experimentally determined crystal structure is good.* Bond lengths and angles are reproduced to within about 0.04Å and 3°. The largest deviations are 0.1Å for the Cu-N_{py} bond in planar [Cu{in-pybox}$(OH_2)]^{2+}$ **C5** and 15° for the twist angle in [Cu{tb-box}$(OH_2)_2]^{2+}$ **C2**. The latter arises in part from a distortion of the coordination plane found experimentally (**X1**) which interferes with the definition of the dihedral angle. The deviation for [Cu{tb-box}$(OH_2)_2]^{2+}$ **X3** is only 3°. The calculated N-Cu-N bite angles Φ are systematically too large by up to 2° for

the aqua complexes. Tetrahedral twists χ (defined as the angle between the normals of the Cu-N and Cu-O planes) for the box systems are correctly predicted as is the slight twist of the $CuCl_2$ plane relative to the pybox plane in pentacoordinate [Cu{tb-pybox}Cl_2] **C4**. The computed structure of the dimeric pybox complex **C6** has the observed Jahn-Teller elongated geometry and [Cu{in-pybox}$(OH_2)]^{2+}$ **C5** is planar as observed in **X5**. It is noteworthy that complex **X5** has triflate oxygen atoms positioned along the notional z-axis at 2.45Å from the copper center. Ligand Field studies suggest the effect from such distant groups would be minimal which was confirmed by the CLFSE/MM calculations.[6] Placing one or both of the triflates on the z-axis does not significantly alter the structure of the rest of the molecule **C5**.

Table 1: Copper(II)-bis(oxazoline) chloro complexes					
Cu{tb-box}Cl_2	Φ(°)	Ψ(°)	χ(°)	Cu-N	Cu-Cl
Calc.**C1**	**94.9**	**112.9**	**53**	**2.00**	**2.20**
Obs.**X1**	**91.3**	**113.9**	**52**	**1.98**	**2.23**

Table 2: Copper(II)-bis(oxazoline) aqua complexes					
Cu{tb-box}$(OH_2)_2(O_3SCF_3)_2$	Φ(°)	Ψ(°)	χ(°)	Cu-N	Cu-OH_2
Calc. C2	**95.9**	**112.8**	**30**	**1.97**	**2.02**
Obs. X2	**94.1**	**112.3**	**45**	**1.94**	**1.98**
Cu{tb-box}$(OH_2)_2(SbF_6)_2$	Φ(°)	Ψ(°)	χ(°)	Cu-N	Cu-OH_2
Calc. C3	**95.9**	**112.8**	**30**	**1.97**	**2.02**
Obs. X3	**94.0**	**111.2**	**33**	**1.91**	**1.99**

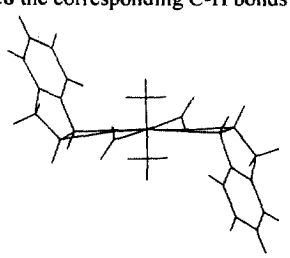
Table 3: Copper(II)-pyridine bis(oxazoline) complexes					
Cu{tb-pybox}Cl_2	Cu-N_{ox}	Cu-N_{py}	N-Cu-N cis	N-Cu-N trans	Cu-Cl
Calc.C4	**2.07**	**1.98**	**79.2**	**158.4**	**2.33**
Obs.X4	**2.11**	**2.01**	**77.7**	**155.3**	**2.27**
Cu{in-pybox}$(OH_2)(O_3SCF_3)_2$	Cu-N_{ox}	Cu-N_{py}	N-Cu-N cis	N-Cu-N trans	Cu-OH_2
Calc.C5	**2.00**	**1.86**	**82.4**	**164.8**	**1.96**
Obs.X5	**2.05**	**1.96**	**79.3**	**158.2**	**1.94**

Computed structures for box-Cu(aqua)$_2$ complexes

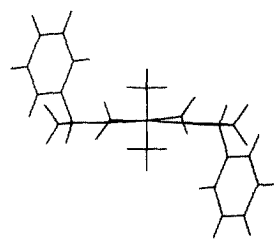
Having demonstrated the validity of the CLFSE/MM method the structures of six bis(oxazoline)Cu(II)-(aqua)$_2$ complexes were calculated (**C7 – C12**). Selected bond angles and lengths are displayed in Table 4.. The experimentally observed stereoselectivity for the reaction of acrylimide (2) and cyclopentadiene at -50°C (Scheme 1) are also tabulated.

Table 4: Calculated structure and observed selectivity	Φ (°)	Ψ (°)	χ (°)	Cu—N	Cu—OH_2	endo(R)/(S)	endo:exo
Dimethyl-in-box **C7**	**95.4**	**112.8**	**9**	**1.98**	**2.01**	**10:1**	**49:1**
Dimethyl-ph-box **C8**	**95.1**	**112.7**	**4**	**1.98**	**2.00**	**1.8:1**	**19:1**
Cyclopropyl-in-box **C9**	**97.7**	**120.6**	**19**	**2.01**	**2.01**	**53:1**	**44:1**
Cyclobutyl-in-box **C10**	**96.3**	**115.8**	**18**	**1.99**	**2.01**	**24:1**	**38:1**
Cyclopentyl-in-box **C11**	**95.7**	**113.2**	**20**	**1.99**	**2.01**	**18:1**	**37:1**
Cyclohexyl-in-box **C12**	**94.9**	**111.5**	**22**	**1.97**	**2.01**	**11:1**	**26:1**

As mentioned previously, for this study the aqua complexes were calculated. Aqua complexes (**C2, C3** χ = 30°) are a good approximation of the imide complexes rather than the chloro complexes (**C1** χ = 53°) on the basis of DFT studies (DFT imide calc.[7] χ = 28°). Scheme 3 shows the calculated structures for the ph-box complex *vs* the in-box complex. These structures clearly show the difference in orientation of the phenyl group in each complex. We have previously attributed the success of the indanyl ligand to the conformational constraint which defines the location of aromatic plane and hence the location of the C_4-H in the 'chiral pocket.' The C_4-H bond is directed towards the aqua ligands in **C7** whereas in **C8** the corresponding C-H bonds are directed away from the substrate binding site.



C7 dimethyl-inbox



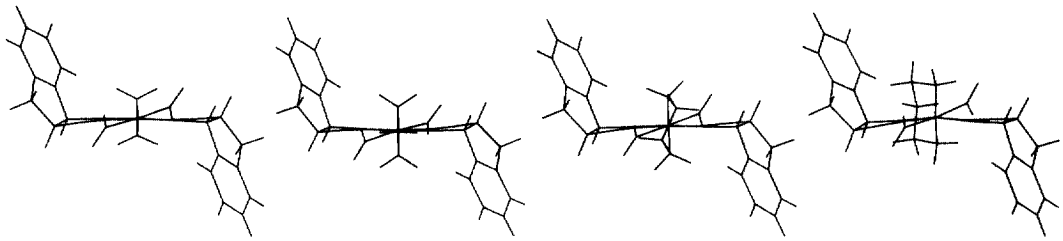
C8 dimethyl-phbox

Scheme 3

These calculations also highlight a substantial difference in tetrahedral twist depending on the nature of the oxazoline C4-substituent. To the best of our knowledge, a ph-box Cu(II) complex has not been characterized crystallographically. The tb-box structure (**C2**) has a larger twist (30°) than either the indanyl **C7** (9°) or the phenyl ligand **C8** (4°). This

observation has implications for other reactions for example this twist (**C2** and **C6** vs **C8**) may be crucial in understanding the sense of induction of ph-box and tb-box for the glyoxylate-ene reaction.[1c] A simple rationale of tetrahedral *vs* square planar geometry no longer seems appropriate in the discussion of reactions involving Cu(II)•box complexes.

Scheme 4 displays the structures of the box•Cu(II) aqua complexes **C9** – **C12**. In our previous study, we have correlated the magnitude of the angle in the *uncomplexed* ligand and the observed enantioselectivity. Using the CLFSE/MM approach we can compare the angle of the *complexed* ligand but more importantly, the value of the bite angle Φ is available. Whilst the trend is still the same – the larger the bite-angleΦ the higher the enantioselectivity – the range of bite-angle values is much narrower (2.8 ° vs 9.1°). An important caveat is the bite-angle can only be correlated in the same structural series *e.g.* the bite angle Φ (and twist χ) for **C7** and **C8** are almost identical but give rise to remarkably different enantiomeric excesses.



C9 cyclopropyl in-box **C10** cyclobutyl in-box **C11** cyclopentyl in-box **C12** cyclohexyl in-box

Scheme 4

Conclusion

New forcefield parameters within the CLFSE/MM framework have been developed specifically for modeling reactions involving bis(oxazoline)Cu(II) complexes. Calculated geometries of structurally characterized complexes of both the box and pybox ligands are in satisfactory agreement with the experimentally determined values. Bis(oxazoline)Cu(II)•aqua complexes were used as models for the catalytically active species. The role of ligand bite-angle was confirmed – although its impact appears to more subtle than proposed originally.

Acknowledgments

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5. $E_{tot} = E_{stretch} + E_{bend} + E_{torsional} + E_{vdw}$ + CLFSE. The CLFSE for a d^n system is given by CLFSE = $\sum_{i=1}^{n} \rho(di)\varepsilon(di)$ $\rho(d_i)$ is the d orbital occupation number and $\varepsilon(d_i)$ is the energy of orbital d_i. The d orbital energies are expressed in terms of the Cellular Ligand Field (CLF) parameters e_λ (where $\lambda = \sigma$, πx or πy) which are in turn expressed as a function of the M-L distance, r. For σ-binding, a linear dependence of e_σ vs r was chosen $e_\sigma = a_0 + a_1 r$ where a_0 and a_1 are empirically derived constant. The resulting values for e_σ are not required, for example, to reproduce the d-d spectrum although this will be roughly true. Similar expressions could be used for $e_{\pi x}$ and $e_{\pi y}$ but the empirical nature of MM allows these π -bonding effects to be subsumed within e_σ.
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7. The DFT calculations were performed with a bis(oxazoline)Cu•(acrylimide) model at the Local Density Approxiamation level of theory using the Amsterdam Density Function program version 2.3.0 with triple-ζ + polarisation STO basis sets. Further studies on other substrates are underway and will be reported in due course.