Latest ligand test 1: i2

1. Make ligand in i2 from Smiles string using AceDRG.

2. REFMAC without ligand. Had to remove OXT from cif, but OXT OK from PDB 1lee.

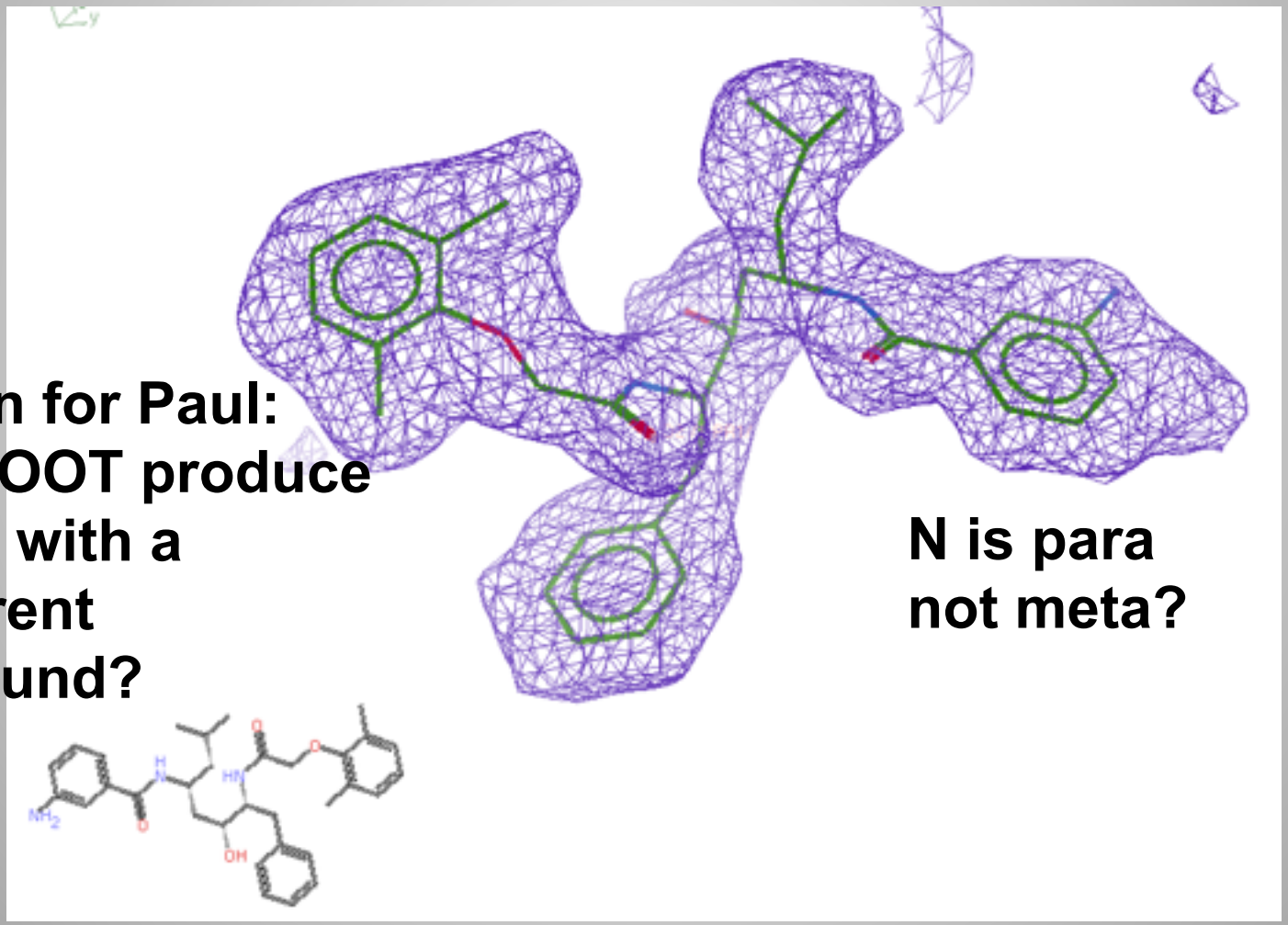
3. COOT. Load REFMAC coordinates without ligand plus output of (1).

4. COOT find ligand.
a) Tried flexible - found no ligand. Managed to move it and fit manually.
b) Switched off flexible - found ligand. Then fitted manually rather easily.

NH2 on the non-aromatic ring is para not meta as Paul also noticed.
We corrected the smile to make N para, then all fitted nicely.
It also looked wrong in the deposited 1lee.

Questions:
How do we rename atoms from the Make ligand task to match R36?
Is there anyway one can download the dictionary with restraints etc. from the PDB?

Latest ligand test 1: i2



Question for Paul: Could COOT produce pictures with a transparent background?

N is para not meta?

Latest ligand test 2: i2

1. Generated dictionary with Make Ligand from smiles.

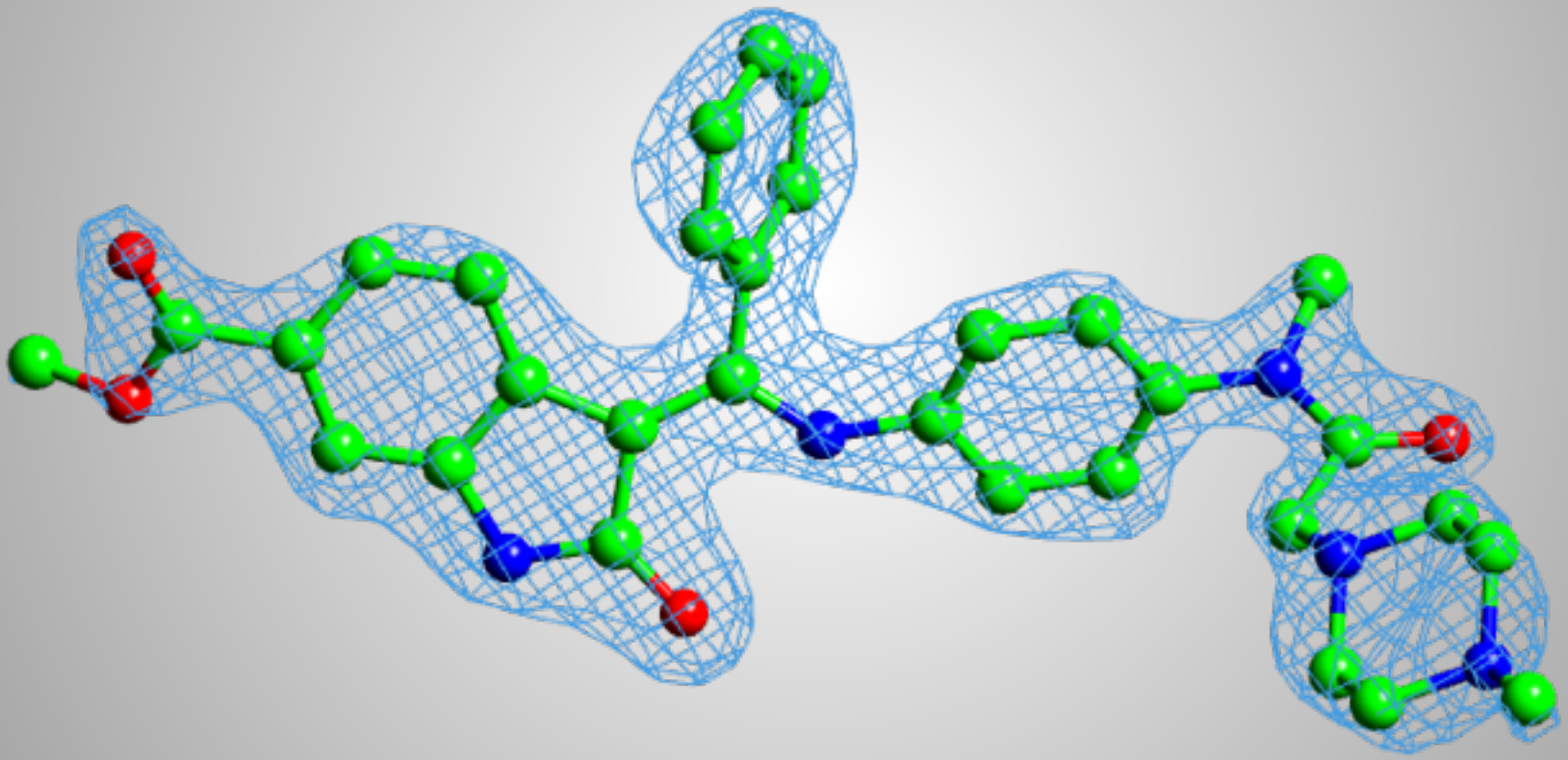
2. REFMAC on ligand free protein.

3. COOT on (1) + (2).
Find ligand.
(a) not flexible. Works well. Easy to optimise.
(b) flexible - fails sadly again.

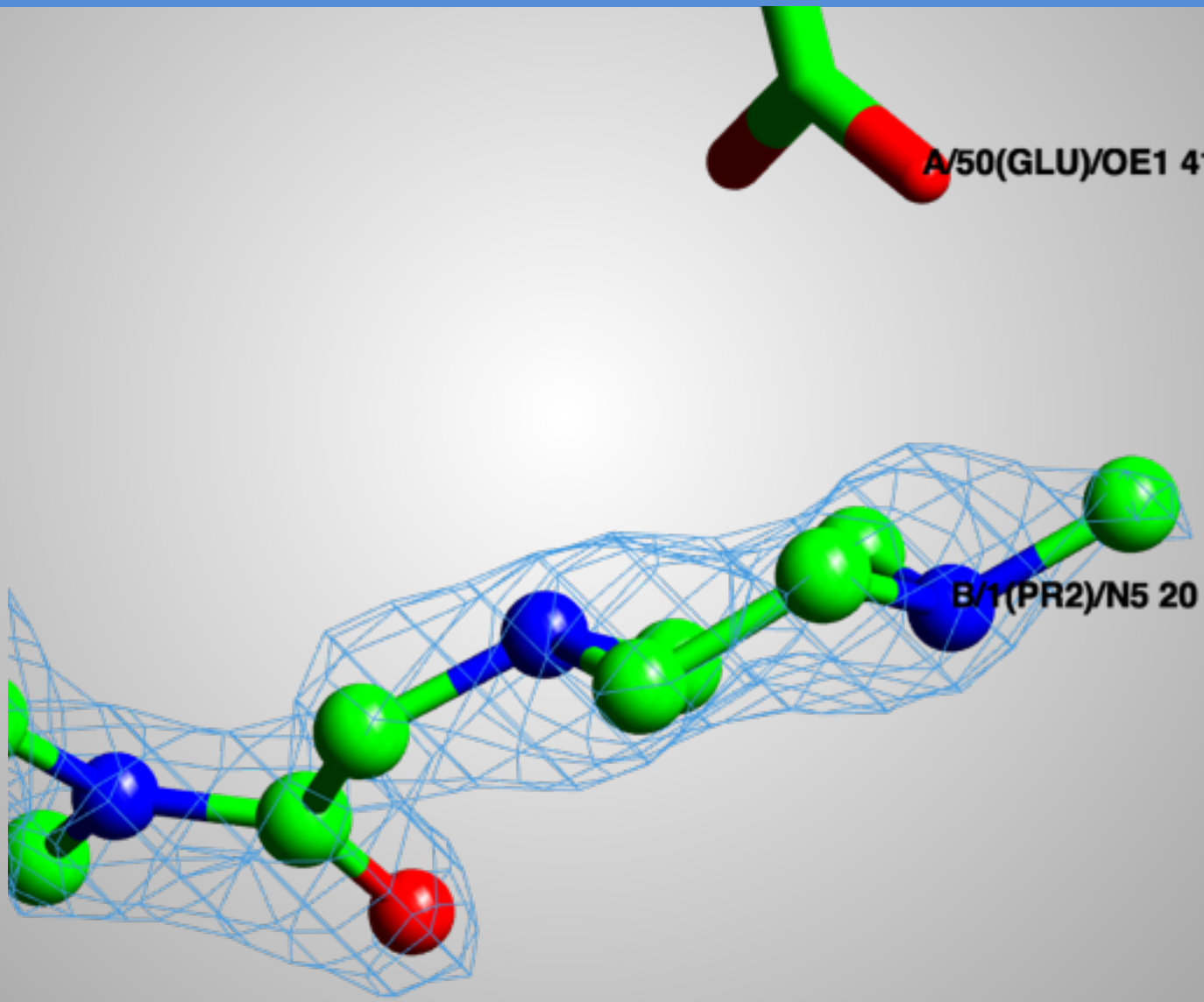
The unsaturated ring system is flipped compared to 5te0. H-bonding to one of the N atoms from a CO2 looks better in 5te0.

Otherwise easy!

Latest ligand test 2: i2



Latest ligand test 2: i2



Test Summary

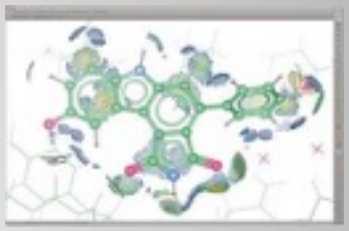
- AceDRG in Make Ligand in i2 doing a good job!
  (Need to update task to remove RDKIT?)
- Easy to use and feed ligand and dictionary into COOT.
- The flexible option in “Find Ligand” in COOT fails.
- Need a name matching capability – see later.

i2, aceDRG and RDKIT

```
=============================================================================
| ACEDRG version:  150                                                      |
| ACEDRG database version:  07                                              |
| RDKit version:  2015.03.1                                                 |
=============================================================================
=============================================================================
| Your job is  generating the dictionary (cif) and coord(pdb) files         |
| for your ligand and/or monomer                                            |
=============================================================================
Input file: tmp.smi
Output dictionary file: AcedrgOut.cif
Input coordinates will be ignored
The system contains atoms of the following elements
C         O         N
COC(=O)c1ccc2c(c1)NC(=O)/C2=C(\Nc1ccc(N(C)C(=O)CN2CCN(C)CC2)cc1)c1ccccc1
A molecule with residue name PR2 is generated
Ligand ID  PR2
Using coords  False
Element to be deleted in the mol is  F
N Bonds  77
Number of chiral centers is  2
Atom N4
Chiraltype  CHI_UNSPECIFIED
-----------------------------------------------
Atom C18 : CIPRank 32
Atom C19 : CIPRank 31
Atom C23 : CIPRank 31
-----------------------------------------------
Chiral sign : both
Atom N5
Chiraltype  CHI_UNSPECIFIED
-----------------------------------------------
Atom C20 : CIPRank 30
Atom C22 : CIPRank 30
Atom C21 : CIPRank 28
-----------------------------------------------
Chiral sign : both
The system contains atoms of the following elements
C         O         N         H
=============================================================================
| Generate the dictionary file using the internal database                  |
=============================================================================
```

Use Case for Ligands: i2

- Ligands are primarily identified and built in COOT or in i2 is it “make Ligand”?.
- Library entry to be used needs both 3D starting coordinates & restraints.
- These are then used in REFMAC - and elsewhere.

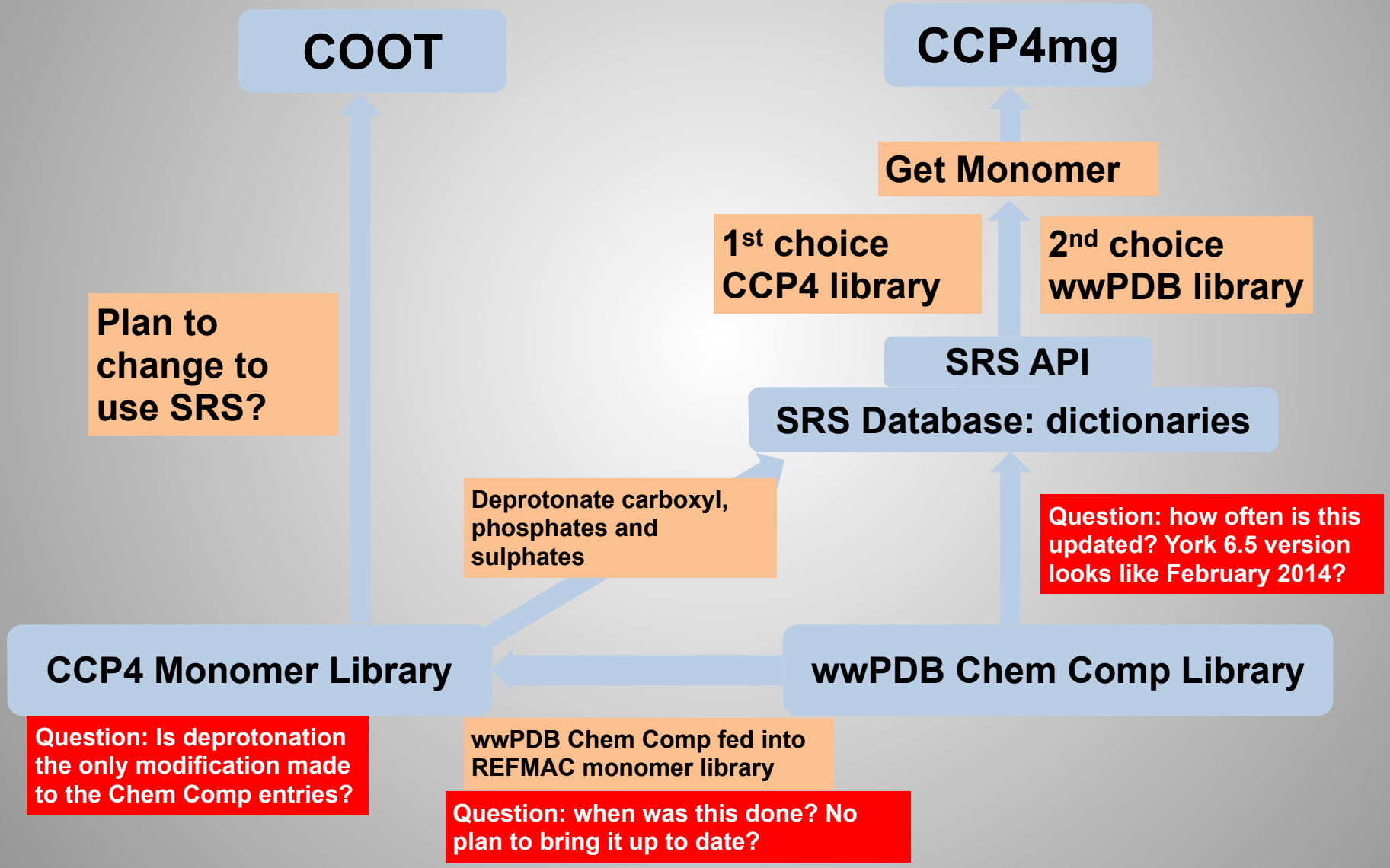


What’s my blob?

Ligand prior knowledge:

- Do I know what is in the crystal? Ligand, solute, crystallisation etc. (Otherwise I will have to think very hard).
- Is there a monomer library entry already? If so how to find & get it. Does the dictionary entry contain both a “good” coordinate set (configuration and conformation) and a good set of restraints? Progress on updating library?
- If not, is there an SRS entry – and the same extra questions?
- If not, we have to construct one. How?
  - Build in i2 using “Make Ligand” Task. Typical start point: SMILES?
  - Build in COOT using Lidia?
  - Build in COOT using JLIGAND?
- How does AceDRG fit into all this? AceDRG now include RDKIT? So “make Ligand” i2 Task needs to be updated.

SRS and Monomers in CCP4



Keith and Stuart's understanding of Garib's CCP4 Monomer Library: $CLIBD_MON/list/mon_lib_list.cif

The monomer library has various sources

1. **Standard amino acids from Engh and Huber? Or more recent?**
2. **Standard RNA/DNA from Parkinson et al 1996 Acta Cryst D52 57-64?**
3. **Others were taken from PDB chem comp but with carboxyl, phosphate and sulphate groups treated differently. These are deprotonated with appropriate adjustments of corresponding functional groups.**

In general functional groups need to be treated properly according pK_a values to make sure that they are protonated or deprotonated when pH is 7. (How to handle different pH is yet another question…).

Do all present monomer library entries need to be recalculated? AceDRG should be able to do this.
Metal containing monomers will cause problems for the foreseeable future. Need to finish treatment of metals in AceDRG.

Questions:

1. **Are restraints right?**
2. **Are coords. right?**

CCP4 Monomer Library Dictionary Entry:

1. **Restraints**
2. **Coordinates (C1)**

Where did restraints come from?

Run REFMAC to optimise geometry of monomer Dictionary entries

New coordinates (C2), based on above dictionary and REFMAC potentials.

Questions:

1. **Do C1 fit restraints?**
2. **Do C2 fit restraints?**
3. **Which fit restraints better C1 or C2?**
4. **More important, do the restraints lead to structures with VdW clashes.**

But next question: Are the restraints right?

Important questions

1. **Status of monomer library updates.**
2. **What on earth do we do about protonation states. Maybe a long term question.**
3. **Metals?**

Options?

1. Do nothing. The ostrich approach.
2. Check all monomer library by hand. Slow….
3. Automatic or semi-automatic approach – probably the only solution. But How to do it? AceDRG is the obvious solution.

Pyrogen Name Matching

- Can Pyrogen match newly generated atom names to those of a “standard” ligand?
- Does this have to be done in COOT?
- How do I do it? Easy?
- Could it be made part of the “Make Ligand” Wrapper?

Reports from Ligand Group

1. **Need a report for January Exec. 1-2 pages. Paul.**

2. **Ligands session at Cosener's.**