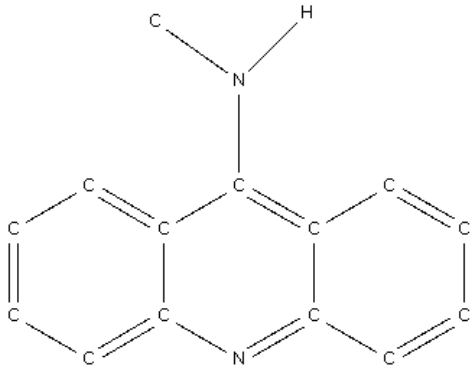
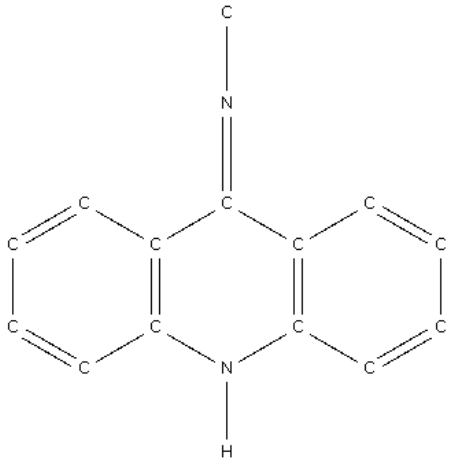
Tutorial 1: Tautomeric Preferences: Aminoacridine versus Iminoacridine

The Example

Aminoacridines are important in a number of therapeutic areas. For example, tacrine (tetrahydroaminoacridine) is an anti-Alzheimer's agent because it inhibits acetylcholinesterase, thereby raising the levels of acetylcholine in the brain. The heterocyclic nitrogen of aminoacridines is basic. If, for example, a modeller wishes to *tune* the basicity of this nitrogen (e.g. to improve physical properties) by introducing substituents onto the acridine ring system. One possible danger is that some substituents might alter not only basicity, but may also alter the preferred tautomer from the amino (C-NHR) to the imino (C=NR) form. This would probably have the radical effect on the binding properties of the molecule, so the modeller needs to know whether there is a danger of this occurring.



aminoacridine



iminoacridine

Objectives

The object of this example is therefore to find out whether any substitution pattern on the aminoacridine system causes a shift in tautomeric equilibrium away from the amino form. Tautomeric preferences can be observed and analysed with a quick survey of the relevant database structures.

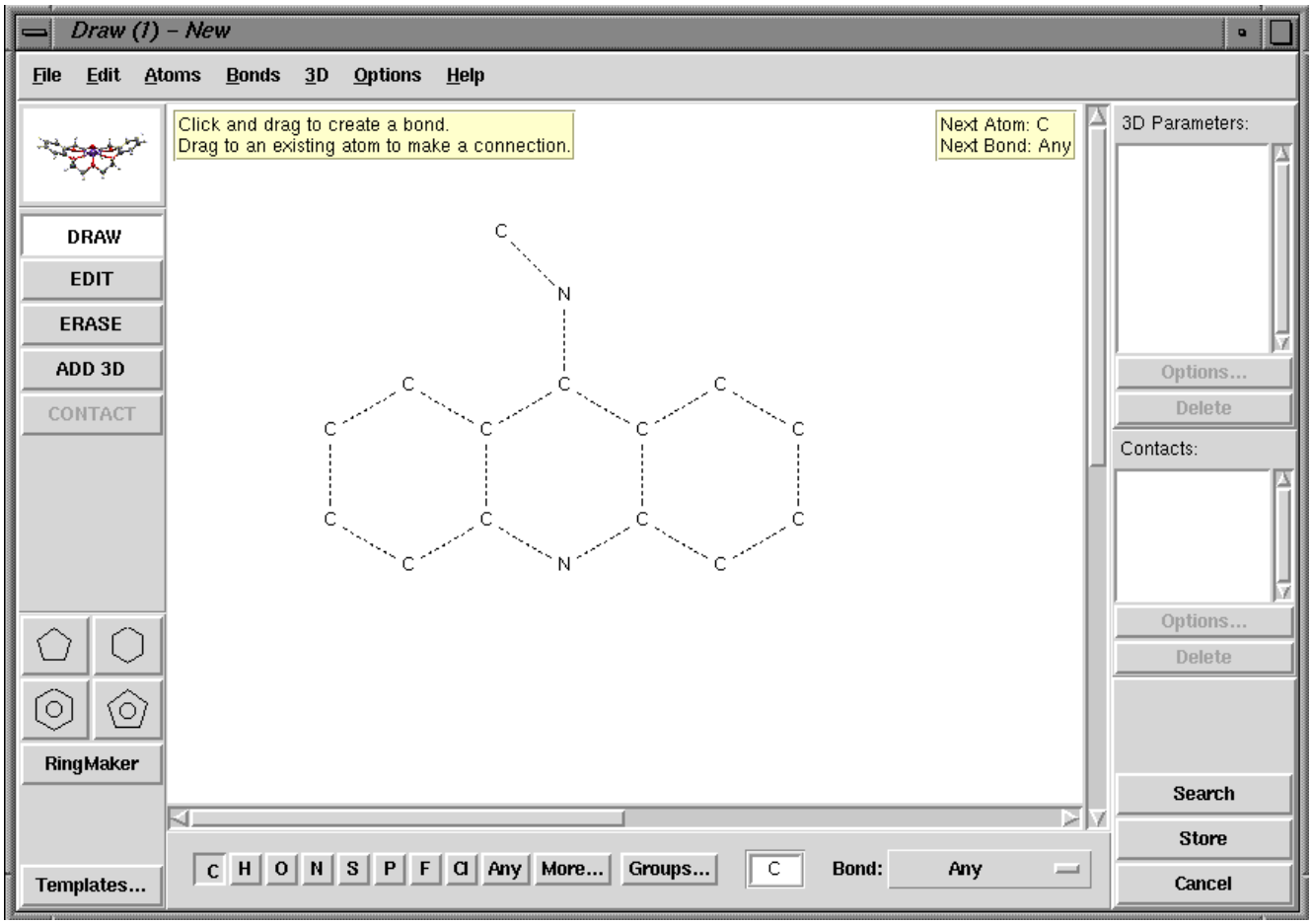
Steps Required

- Draw the chemical fragment of aminoacridine.
- Introduce constraints to remove unwanted entries.
- Run the search and analyse the results by visual inspection (geometric tests can also be used).

Menu Commands Required

1. Start ConQuest and hit the **Draw** button to open the *Draw* window.

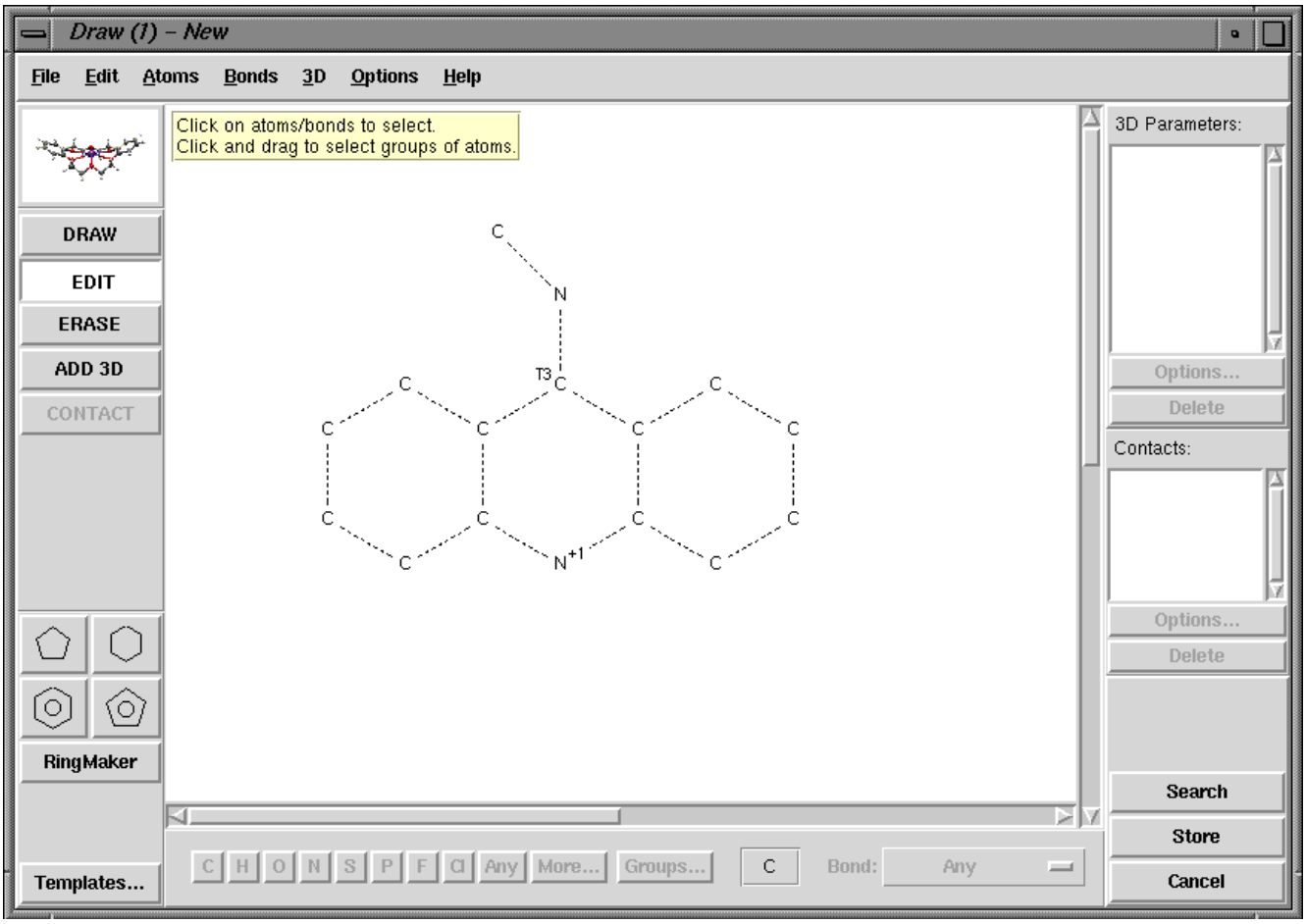
2. Draw the substructure in the usual way, as shown in Tutorial 1.
   - All tautomers of the aminoacridine fragment can be searched for with one general search query by using ***Any*** bond type.



   - Hit **Store** to transfer the query to the *Build Queries* page.

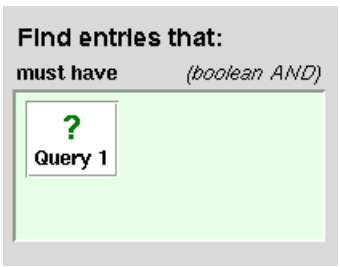
3. Edit the query you have just created, to exclude those entries we don't wish to include in the search (e.g. charged molecules).
   - Click on **Edit...** , on the right hand side of your query, and this launches the *Draw* window containing the query you have just created.
   - Put a charge of +1 on the nitrogen in the ring, e.g. by right-clicking on the N atom and selecting **Charge, Positive** and then **+1** from the resulting pull-down menu.
   - Restrict the coordination number of the apex carbon atom in the central ring to 3, e.g. by right-

clicking on the C atom and selecting **Number of Bonded Atoms** and then **3**.

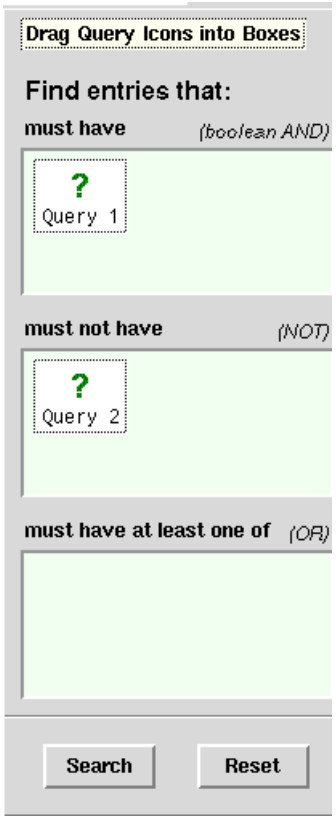


- Hit **Store** to transfer the query to the *Build Queries* page. A pop-up menu asks if you wish to *Overwrite existing Query*, hit **No**.

4. Combine the queries.
   - Click on *Combine Queries*.
   - Position the cursor over the top query icon (i.e. the white square next to the initial query, labelled *Query 1*), press down on the left-hand mouse button, and drag the icon into the box labelled *must have*:



- Drag the second query icon (*Query 2*) into the box labelled *must not have*.



5. Run the search without setting any filters and view the hit list.
   - Hit the **Search** button at the bottom left-hand corner of the window.
   - The pop-up confirms that the search will be for structures that satisfy Query 1 but do not satisfy Query 2.
   - Hit **Start Search** to begin the search.

6. Viewing the data.
   - Browse through the hits. You should notice a marked preference for the aminoacridine tautomer while browsing. The imino form can exist and it is worth looking at the type of situation in which they do occur (e.g. CUHREC10 and CUHRIG10), some exhibit a beta-nitrogen ligand and in general the introduction of strongly electron-withdrawing substituents onto the ring system can have a dramatic effect on the form adopted.

This ends the tutorial