

User Guide for the HELM Web Editor

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Intended Audience

This document explains the essential functions of the HELM editor.

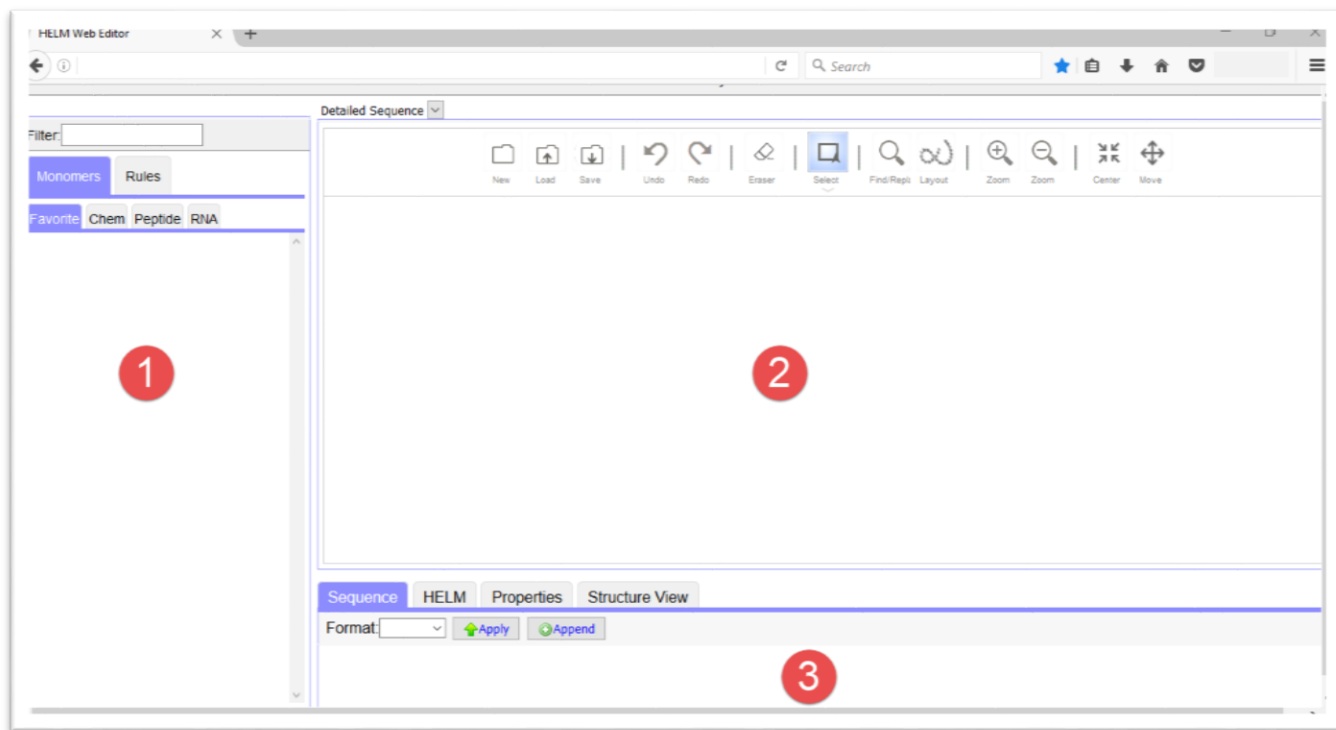
It assumes familiarity with the basics of the HELM notation and common types of macro-molecules, such as, nucleotides and peptides.

For more information on the HELM notation, please see the HELM website:

www.openHELM.org

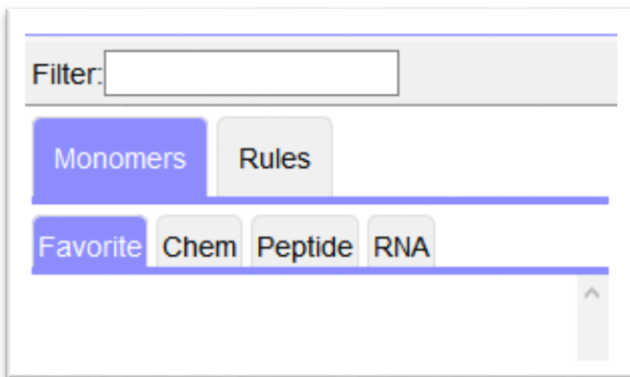


Quick reference guide to the main screen



1. Monomer browser
 - a. Provides access to monomers required to build macromolecules.
2. Canvas
 - a. Drawing area where you can place monomers and build macromolecules.
3. Viewing area
 - a. Provides alternative views of the molecule such as natural analog sequence, HELM, properties such as mol wt and the atom-bond structure.

Monomer Browser

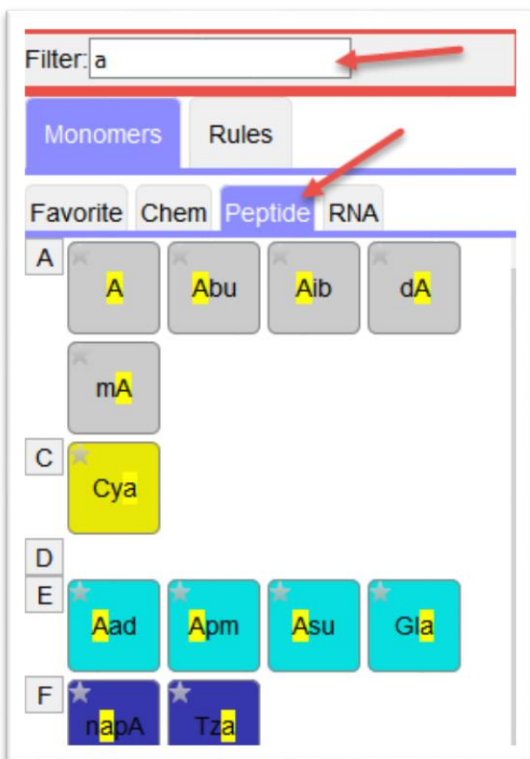


The monomer browser provides access to the monomer library, which is divided into chemical monomers, peptide and nucleotide monomers. The tabs are used to browse the library.

Frequently used monomers can be displayed in the favorites tab and frequently used functions can be saved under the Rules tab.

Filtering the monomer set

The Filter box can be used to search for monomers.

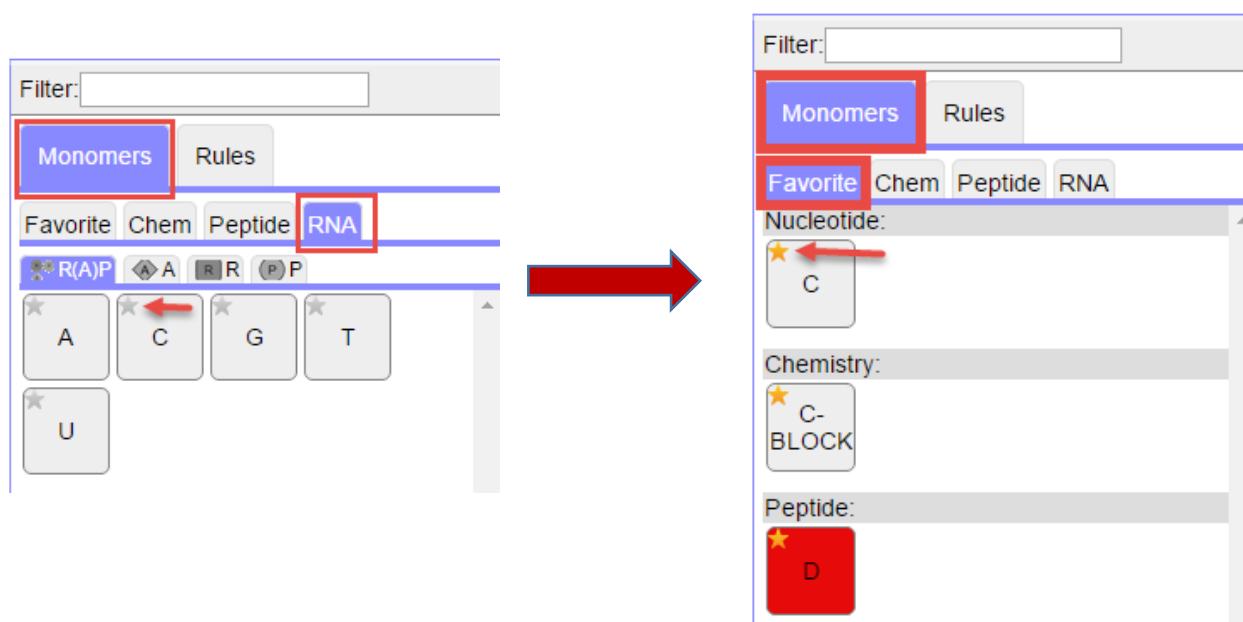


To search for a monomer, choose the tab for the type of monomer, then, in the Filter box, type letters or numbers from the monomer symbol.

Note: Entering lower case letters will display items with either upper or lower case letters anywhere in the code.

Using Monomer Favorites

Frequently used monomers can be saved under the Favorite tab.



To create a favorite:

- Select the desired monomer under the Chem, Peptide or RNA tabs.
- Click on the star symbol in the upper left corner of the monomer icon.
- The star will turn from grey to yellow and the monomer icon will be saved in the Favorite tab.

Click the yellow star to deselect a Favorite.

Browsing the different monomer categories

Chem and peptides

Choose the Chem or peptide tab under the Monomer tab to display the different lists. The monomers will be displayed in the area below. Peptide structures are categorized according to their natural analog.

The screenshot shows a web interface for selecting monomers. At the top, there is a 'Filter:' input field. Below it are two tabs: 'Monomers' (highlighted with a red box) and 'Rules'. Under the 'Monomers' tab, there are four sub-tabs: 'Favorite', 'Chem' (highlighted with a red box), 'Peptide', and 'RNA'. A grid of monomer icons is displayed, each with a star icon in the top-left corner. The icons include: R, A6OH, Alexa, Az, C-BLOCK, Cys-BLOCK, EG, hxy, MCC, N-BLOCK, PEG2, sDBL, SMCC, SMPEG, and SS3. A red arrow points to the 'Az' icon, which has triggered a tooltip. The tooltip is titled 'Azide' and shows the chemical structure of an azide group attached to a chain, with a red oxygen atom and a blue nitrogen atom. Below the structure, it says 'R1= OH'. To the right of the main interface is a 'Detailed Sequence' dropdown menu.

A tooltip of the chemical structure will appear by mouse-hovering over the chemical icon.


Filter:

Monomers Rules

Favorite Chem Peptide RNA

A	A	dA	mA	meA
C	C	dC	meC	seC
D	D	dD	meD	
E	E	dE	meE	
F	F	dF	meF	

N-Methyl-Alanine

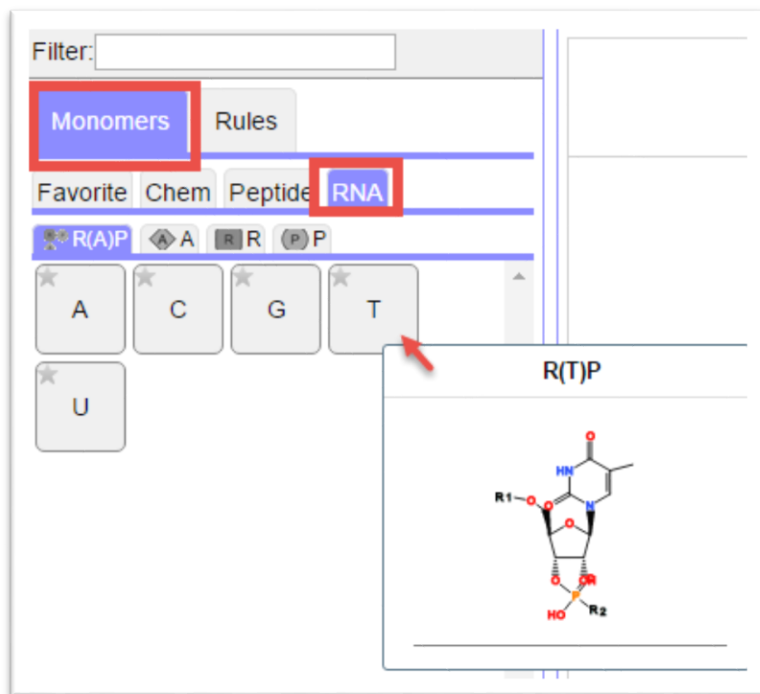


R2= OH
R1= H

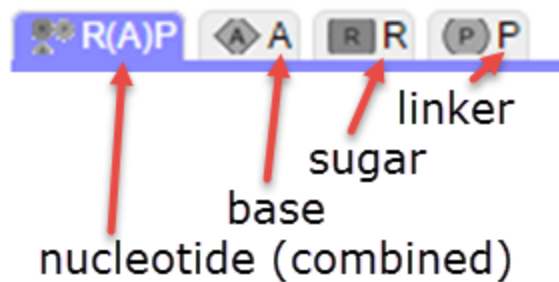
The image shows a software interface for selecting nucleotides. At the top, there is a 'Filter' input field. Below it are two tabs: 'Monomers' (highlighted in blue) and 'Rules'. Under the 'Monomers' tab, there are sub-tabs for 'Favorite', 'Chem', 'Peptide', and 'RNA'. The 'Peptide' sub-tab is highlighted in red. A grid of nucleotide buttons is displayed, organized by amino acid (A, C, D, E, F) and modified forms (A, dA, mA, meA). A red arrow points from the 'meA' button to a pop-up window. The pop-up window displays the chemical structure of N-Methyl-Alanine, which is a central carbon atom bonded to a methyl group (wedge), a hydrogen atom (dash), an N-methyl group (R1), and a carboxyl group (R2). Below the structure, it specifies R2= OH and R1= H.

RNA

Nucleotides have subcategories as well as the main tab.



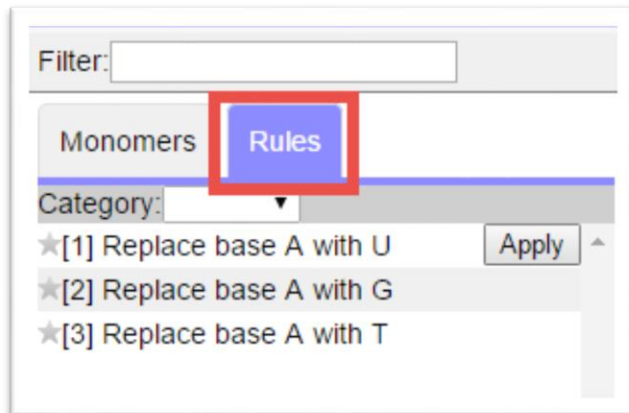
Choose the RNA tab under the Monomer tab to display the nucleotide list.



There are four tabs under the RNA tab:

- 1) R(A)P: Choose this tab to display the nucleotide (combined) options.
- 2) A: Choose this tab to display all the bases.
- 3) R: Choose this tab to display all the sugars.
- 4) P: Choose this tab to display all the linkers.

Rules



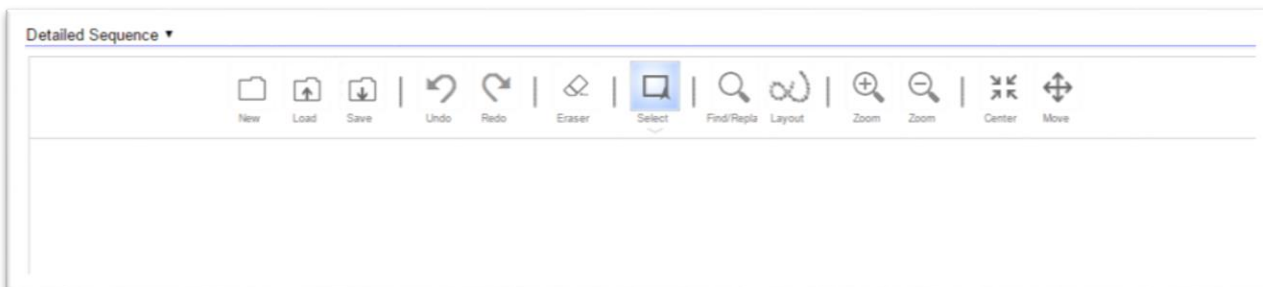
Choose the Rules tab to display preset rules.

Select a Category of preset rules from the Category dropdown menu.

Click the Apply button to apply the rule.

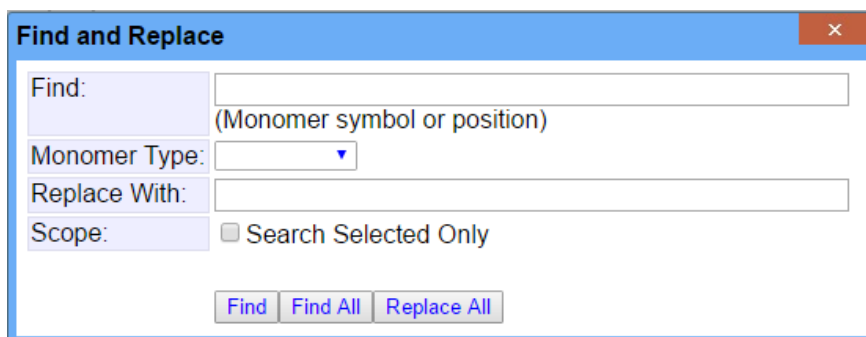
Canvas

The canvas is the main drawing area of the editor and contains a number of buttons to help the user construct a macromolecule.



Buttons:

- New: Clears the contents in the canvas.
- Load: Loads a HELM or xHELM file.
- Save: Save contents as a HELM or xHELM file.
- Undo/Redo: To undo or redo a change on the canvas.
- Eraser: Erases a selected monomer.
- Select: Dropdown menu with Select, Lasso, Fragment or All tools to capture some or all of the monomers displayed on the canvas.
- Find/Replace: To find a monomer or to replace a monomer with another.

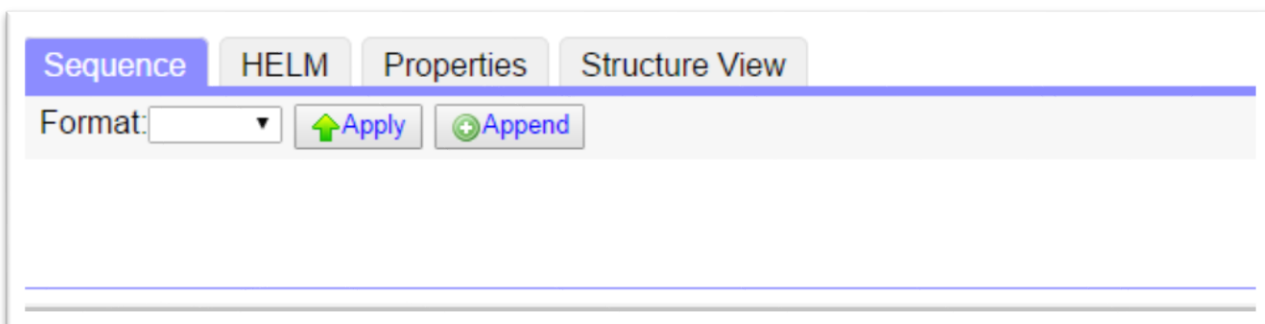


- Layout: Cleans up monomer display.
- Zoom +/-: Makes selected monomers larger or smaller.
- Center: Centers monomer display on canvas and displays zoomed monomers at default size.

- Move: Moves all monomers around the canvas. Also used to enlarge an area of a structure. Select move and use the mouse-wheel to zoom in and out on a structure. Mouse-click on area on which to focus.

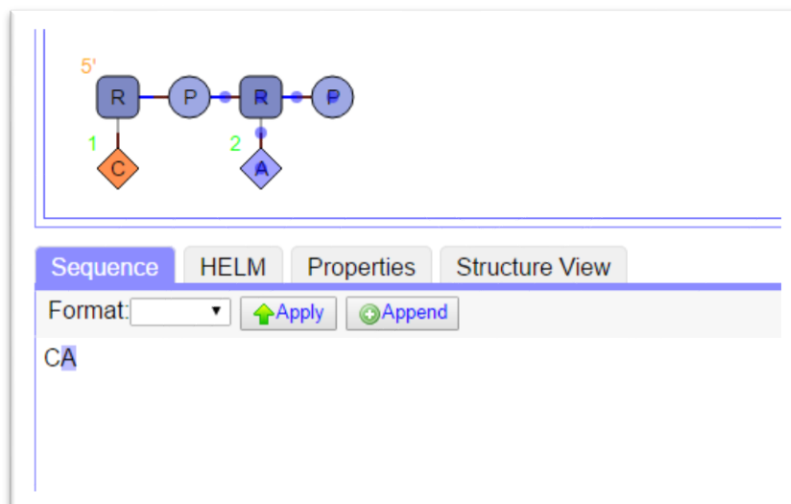
Choose Detailed Sequence/Sequence from the dropdown menu to switch the display of the Canvas and Viewing Area.

Viewing area



See a sequence view of a molecule or the component view that provides details such as Mol. Wt., Mol. Formula etc.

Sequence viewing

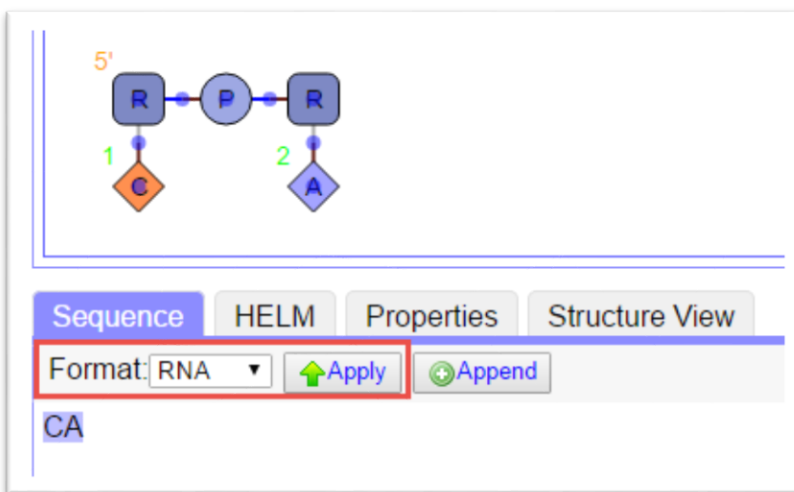


Choose the Sequence tab to display the sequence of monomers drawn on the canvas.

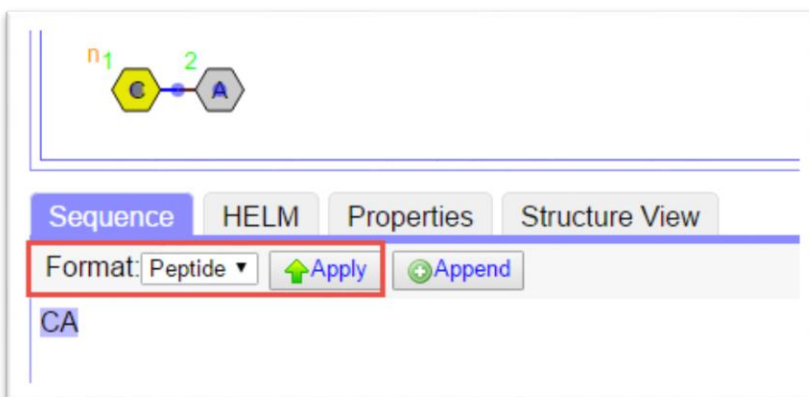
In the example sequence view the Nucleotide 'A' has been selected on the canvas and the corresponding nucleotide in the sequence display is highlighted.

Adding monomers via the sequence tab

A sequence can also be imputed directly by writing the sequence in the Sequence Viewing area or copying and pasting a sequence into the Viewing area and clicking Apply. Choose the format before applying!



OR



You can add to an existing structure using the append function. This will add the new sequence to the canvas and you can then attach them together using normal drawing functionality.

The screenshot shows two RNA structures in a 2D representation. Each structure consists of a 5' phosphate group (P) connected to a ribose sugar (R), which is then connected to another phosphate group (P). The first structure has a cytosine (C) base attached to the first ribose sugar, and the second structure has an adenine (A) base attached to the second ribose sugar. Below the structures is a control panel with tabs for 'Sequence', 'HELM', 'Properties', and 'Structure View'. The 'Sequence' tab is active, showing a 'Format' dropdown set to 'RNA', an 'Apply' button, and an 'Append' button highlighted with a red box. Below the buttons, the sequence 'CA CA' is displayed.

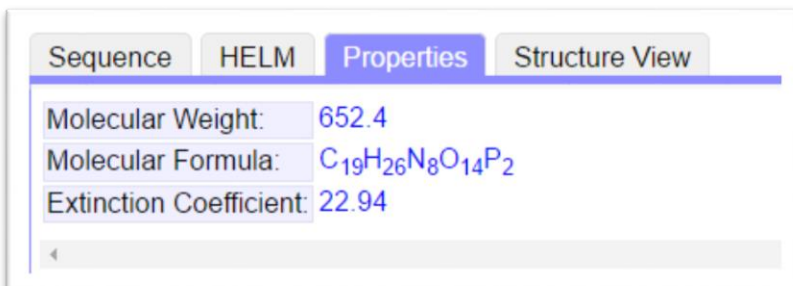
HELM notation

Choose the HELM tab to display the HELM notation. The notation for the sequence 'CA' is displayed with 'A' highlighted because this is highlighted on the canvas.

The screenshot shows the same software interface with the 'HELM' tab selected. The 'Apply' and 'Append' buttons are visible. Below them, the HELM notation 'RNA1{R(C)P.R(A)P}\$\$\$\$V2.0' is displayed, with the 'A' in 'R(A)' highlighted in blue.

Properties

Choose the Properties tab to display the Molecular Weight, Molecular Formula and Extinction Coefficient for the entire sequence.

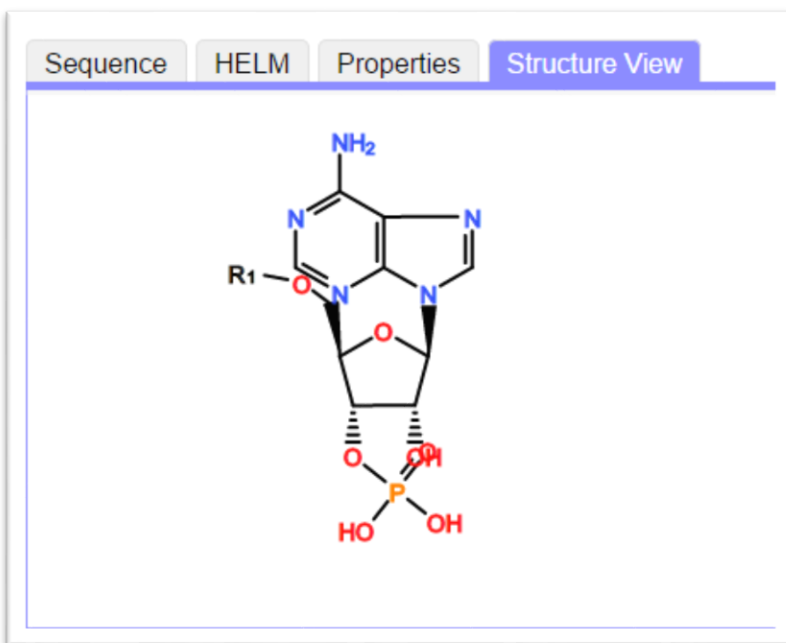


The screenshot shows a software interface with four tabs: "Sequence", "HELM", "Properties", and "Structure View". The "Properties" tab is selected and highlighted in blue. Below the tabs, the following information is displayed:

Molecular Weight:	652.4
Molecular Formula:	$C_{19}H_{26}N_8O_{14}P_2$
Extinction Coefficient:	22.94

Structure View

Choose Structure View to see the structure of the selected monomer (in this case A).



The Viewing area can be enlarged by dragging the line separating the Canvas and Viewing area up or down.

All or part of a structure can be viewed by using the Select button to choose the area to view.

Creating a new molecule

Using the drawing Canvas

Explore all the available monomers under the 'Chem', 'Peptide' and 'RNA' tabs.

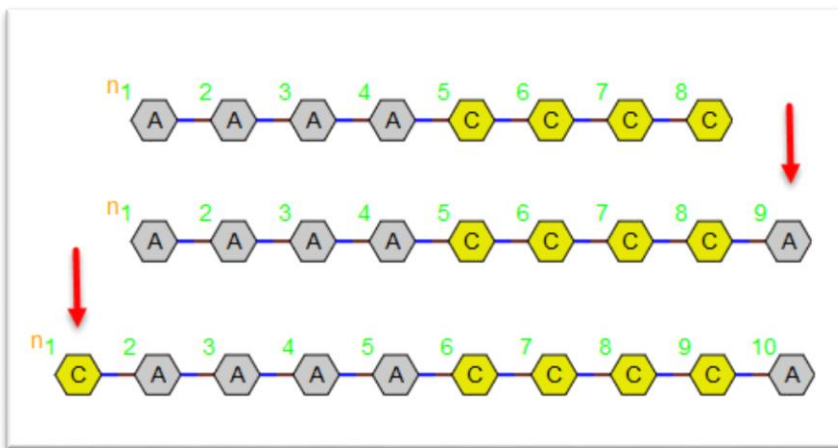
There are three ways to add a monomer to the Canvas:

- 1) Click on the monomer in the Monomer Browser, and drag to the drawing Canvas.
- 2) Click on the monomer then click in the Canvas.
- 3) Write a sequence in the Viewing area.

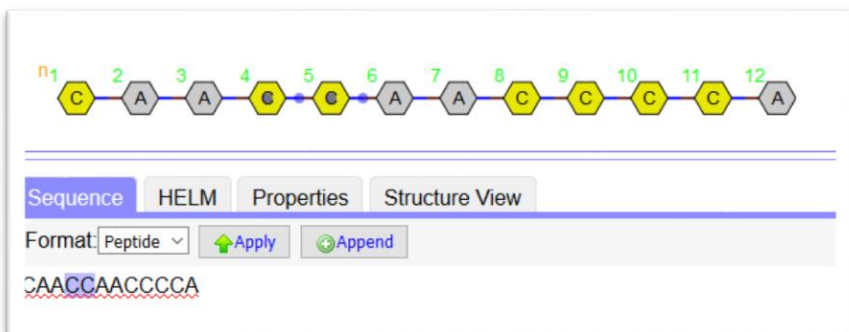
After adding the first monomer, the next can be added in the same way.

A monomer on the Canvas can be changed to another monomer of the same type in three ways:

1. Highlight the replacement monomer in the Monomer Browser, hover over an existing monomer on the Canvas and click on the monomer,
2. Hover over an existing monomer on the Canvas and using the keyboard type the letter representing the monomer,
3. Highlight the replacement monomer in the Monomer Browser, hover over an existing monomer on the Canvas, left-mouse-click and drag left or right away from the monomer. In the example, an 'A' is added to the right, and then, a 'C' is added to the left. Note that the numbering changes when a monomer is added to the left.

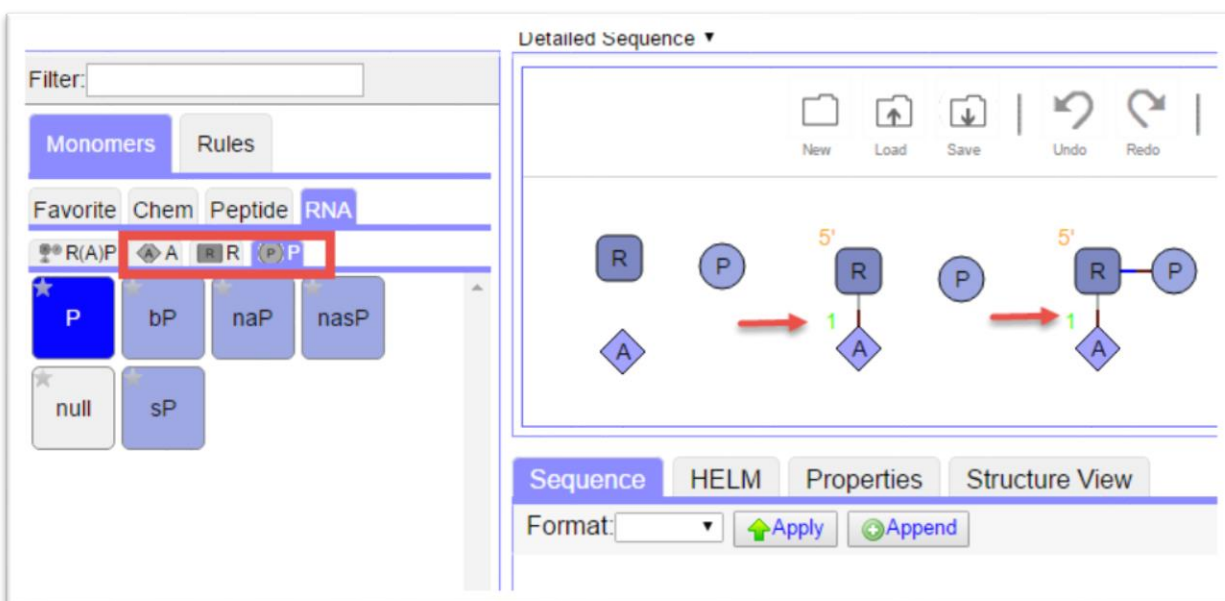


Monomers can also be added to any position in the sequence by adding them into the sequence in the Sequence Viewing area.

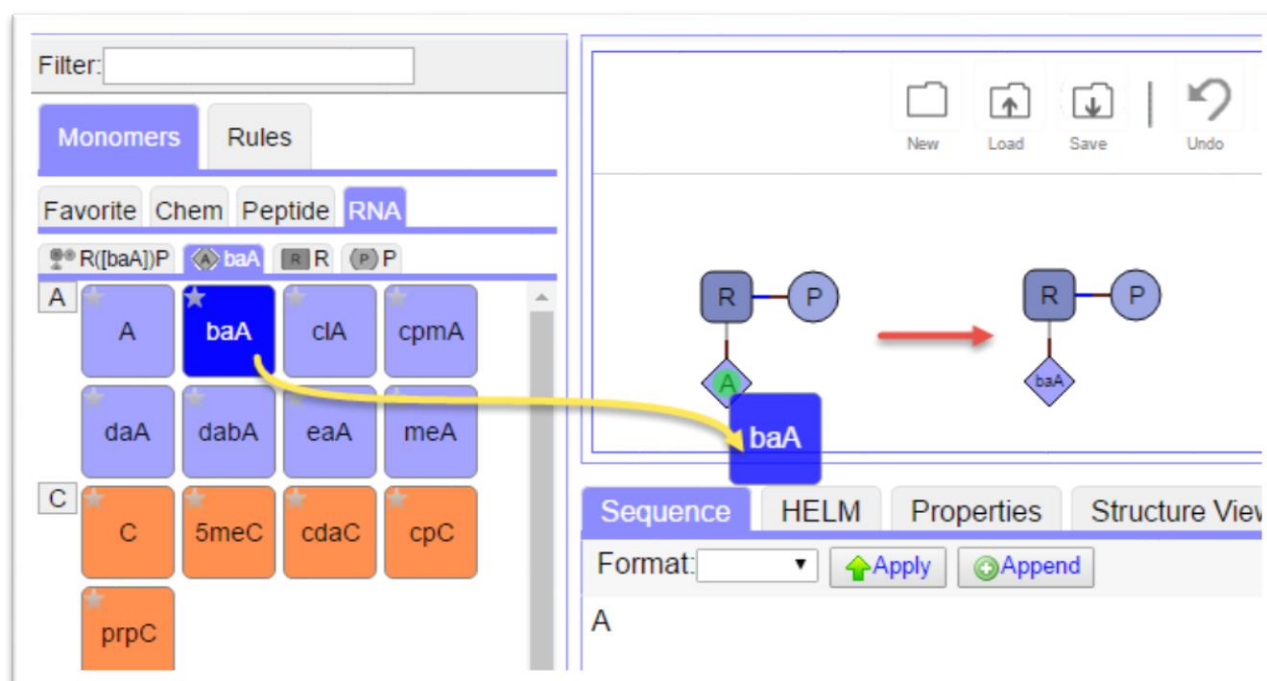
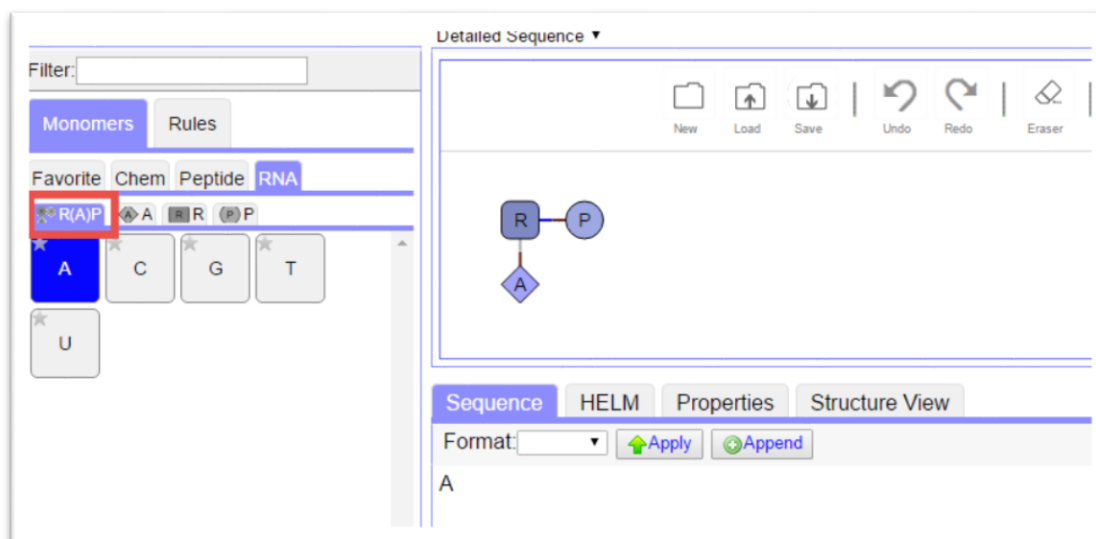


Nucleotides can be added to the Canvas in two ways:

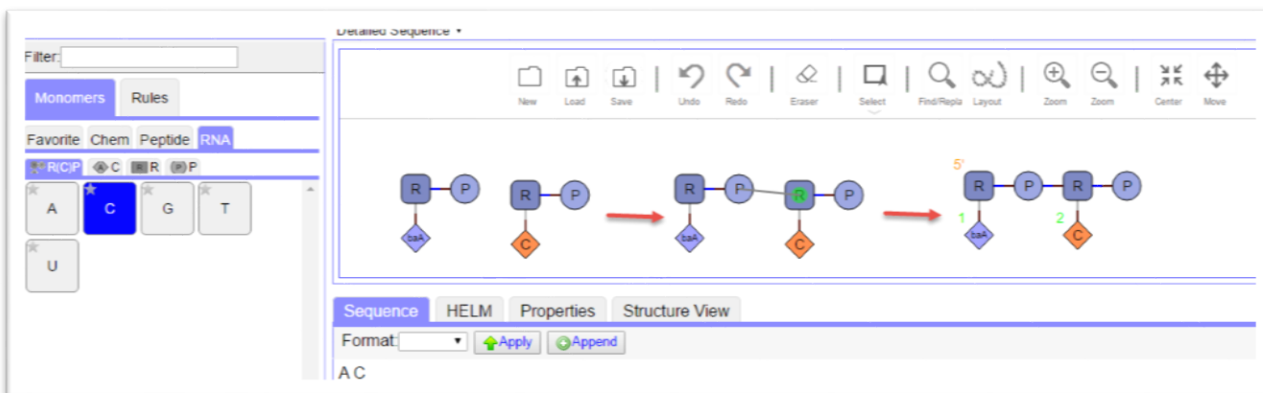
- 1) Linkers, Bases, and Sugars from the RNA tab can be placed directly onto the canvas and individually linked. Note that the 5' end of the sequence is indicated.



- 2) The Nucleotide can be added from under the Nucleotide (Combined) tab and then the individual linkers, bases and sugars can be changed by clicking on the desired linker, base or sugar in the monomer list then dragging to the desired position or clicking on the desired position.



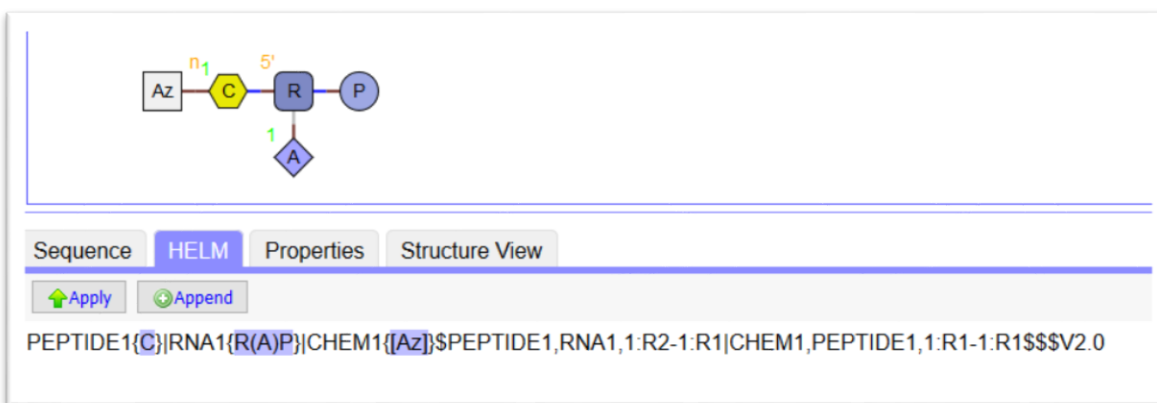
Once there is more than one monomer on the screen, a bond can be drawn between them by selecting one monomer, left-mouse-click, hold and drag to the second monomer.



Please note the following principles:

- Connections are drawn from N to C terminus for peptides and from 5'→3' for the nucleotides.
- If monomers cannot be connected a dialogue box will appear with a message.
- If two sugars are connected, the phosphate linker is automatically inserted.

Conjugates



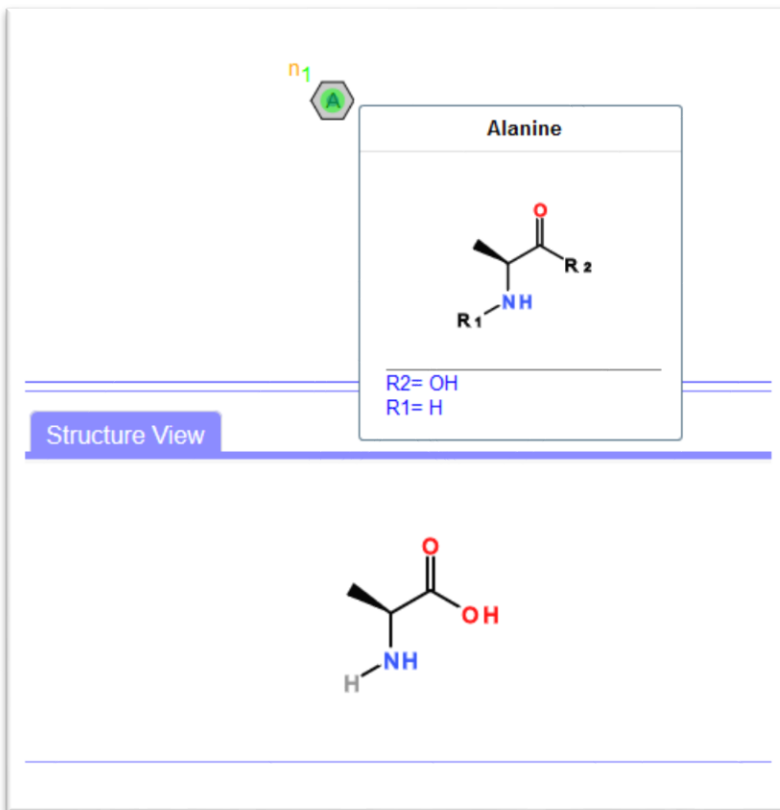
Conjugates can be drawn by selecting chemicals, peptides and nucleotides from the Monomer Browser and linking the monomers together.

If monomers cannot be connected a dialogue box will appear with a message.

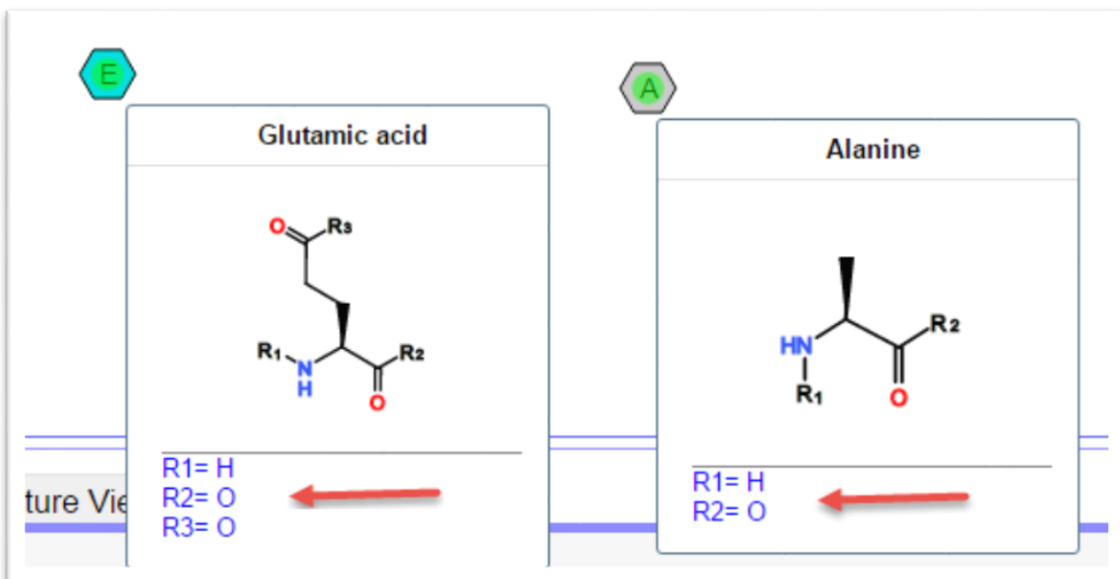
R-Groups

It is important to understand the r-groups available in a monomer. The tooltip structure will show you where they are in the structure itself and the list at the bottom of the box shows the capping groups for each R group.

R groups are shown as capped in the Viewing area\Structure View tab. In this Alanine example R1 is H-capped.



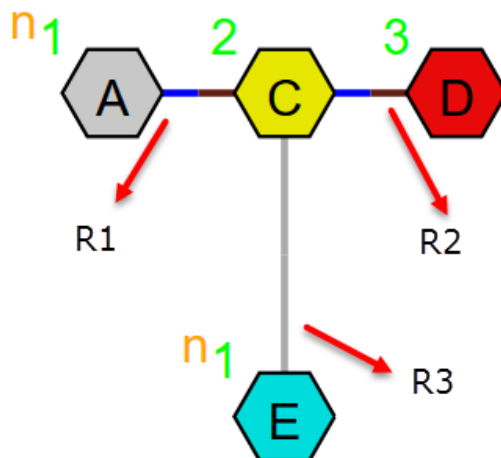
Monomers in the middle of a chain are typically linked to two other monomers, however certain monomers can form additional bonds. For example, Alanine (A) has two R groups (R1 and R2) with which to connect to other monomers, while Glutamic Acid (E) has three R groups (R1, R2 and R3).



In this example, 'E' is attached to 'C'. When drawing the connecting bond between 'C' and 'E' a pop-up message will appear. The available connecting points for the two monomers will be displayed in the dropdown menu. There is only one available connecting point for C2 (R3). There are three available connecting point for E (R1, R2 and R3).

The screenshot shows a software interface for building a peptide sequence. A 'Choose Connecting Points' dialog box is open, showing the chemical structures of Glutamic acid (labeled 'E') and Alanine (labeled 'C2'). The Glutamic acid structure has substituents R1, R2, and R3. The Alanine structure has substituents R1 and R2. Below the structures are two dropdown menus. The first dropdown menu is for 'E' and shows three options: R1, R2, and R3. The second dropdown menu is for 'C2' and shows only one option: R3. An 'OK' button is at the bottom of the dialog.

The number of attachment points of a monomer defines the number of covalent bonds in which the monomer can be involved.



The Connection points are indicated by color: blue for R1, orange for R2, and gray for R3. The n-terminal is indicated by 'n'.

Working with structures

Monomers or bonds can be removed by mouse-hovering over them and hitting delete. Also, use the Select button to select the monomers to delete and hit delete.

To replace any of the monomers, drag a replacement monomer from the monomer browser and drop it onto the current monomer (as described previously), so long as their type and attachment points allow the replacement.

Replacing monomers

If a sequence contains a consistently modified monomer there are two options for updating it.

1. Use the Rules tab from the monomer browser (as described previously) to perform a search and/or replace the monomer.
2. Use the Find/Replace button (as described previously) in the Canvas menu to find a monomer or to replace a monomer with another.

Using the Find/replace box:

Find:

Enter the monomer in the Find box, choose the Monomer Type from the dropdown menu, and click Find to find the first monomer in a sequence or click the Find All button to find all monomers in a sequence. A pop-up message will display the number of monomers found. The monomers found will be highlighted in the Sequence or HELM Viewing area.

Replace:

Enter the monomer in the Find box, choose the Monomer Type from the dropdown menu, enter the replacement monomer in the Replace With box and click the Replace All button. A pop-up message will display the number of monomers replaced.

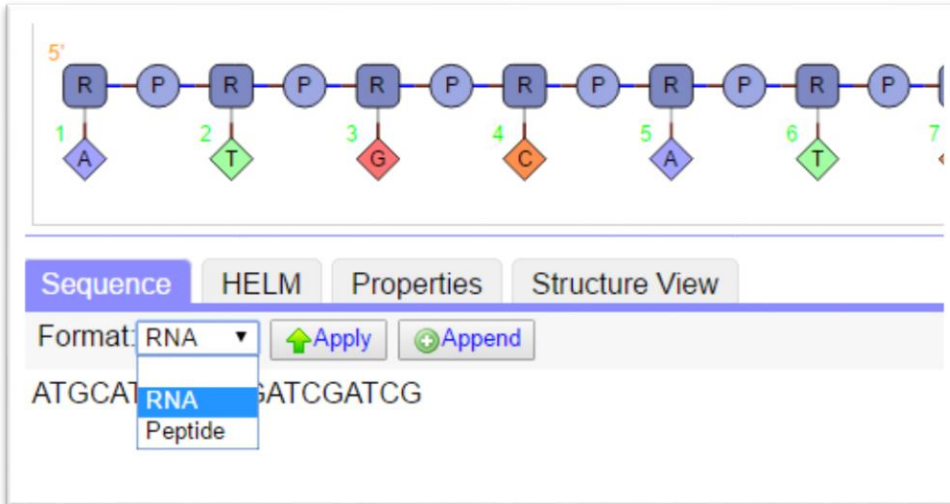
If only finding/replacing in a selected area, select that area using the Select button and check the Search Selected Only box.

The screenshot illustrates the 'Find and Replace' functionality in a software interface. The main window displays a sequence of amino acids: A, E, A, C, A, D, A, C, A, C, A, E, D, A, C, A. A 'Find and Replace' dialog box is open, showing the following settings: 'Find:' is set to 'A', 'Monomer Type:' is set to 'Amino Acid', 'Replace With:' is set to 'I', and 'Scope:' is set to 'Search Selected Only' (unchecked). Below the dialog, the sequence viewer shows the sequence 'AEACADACACAEDACA' with the first 'A' highlighted. A red arrow points from this 'A' to the 'Find and Replace' dialog box. Below the dialog, the sequence viewer shows the sequence 'IEICIDICIEDICI' with the first 'I' highlighted.

Building a molecule using the sequence

Build new molecules by entering sequence information directly in the Viewing area, rather than dragging and dropping individual monomers, a process which is slow for larger polymers.

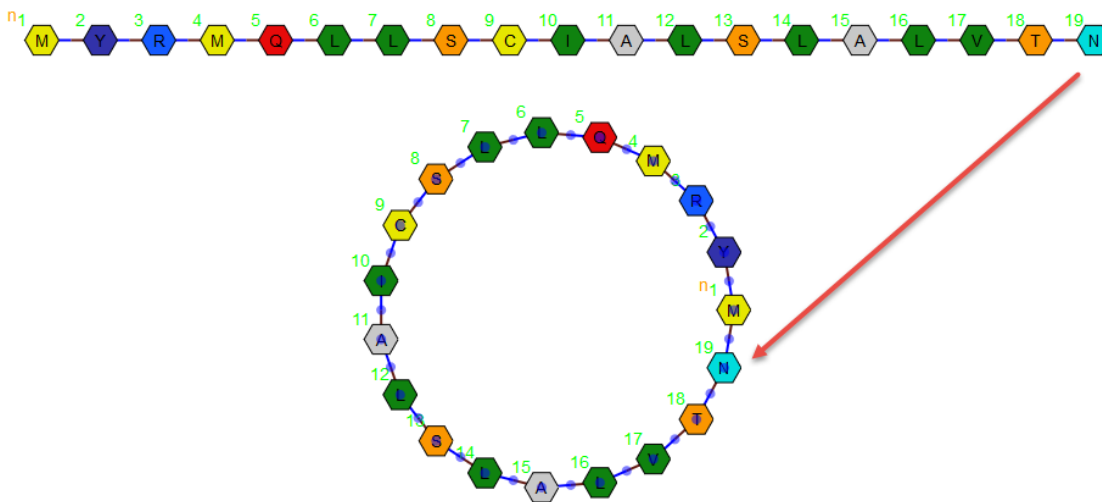
There are two sequence loading options: nucleotide sequence (RNA) and peptide sequence (Peptide).



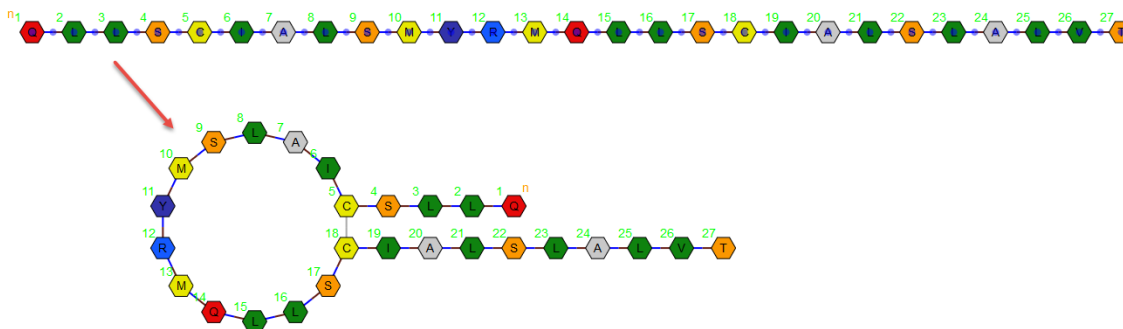
Cyclizing a sequence

To form a cyclic sequence, add a bond between two monomers that have suitable attachment points.

To create a backbone cycle, connect the first and the last monomers. In this example connect 'M', the first peptide, with 'N', the 19th peptide.



To create an intra-chain bridge, connect two monomers in the same sequence, that have more than two attachment points. Once the bond is added, the molecule will rearrange to form a cycle, and show the link as appropriately as possible.



Saving and loading macromolecules

Once a new molecule is created or an existing monomer is modified, there are two formats to save and load the molecule data (using the Save and Load buttons in the Canvas), the HELM notation and the xHELM notation.

HELM notation

The HELM notation is the native data format of the HELM editor. The format is described extensively on the OpenHELM.org website. If you want to use your molecules mainly within your organization, HELM is the format of choice. It is a very compact and clear, but it relies on a common set of monomers for the molecules.

Exchangeable HELM notation (xHELM)

The xHELM format was developed as the “portable” version of HELM. Like the HELM notation, xHELM is a unique notation. It contains the normal HELM notation in addition to the full set of monomers contained within the molecule. This is useful if you want to exchange your molecule data with other organizations, especially if you use non-standard monomers.