Structure searching: what you get is what you wanted.

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The Need

- Represent chemical structures in computer readable form
- Translate between computer representation and human readable form
- Store structures in a database
- Retrieve the structures selectively, accurately, and reproducibly

The Fundamental Problem

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- A molecule is described by a collection of molecular orbitals and atoms
- Difficult to interpret this representation
  - Human and machine
- Representation based on molecular orbitals is not practical

Chemical Structure Identifiers

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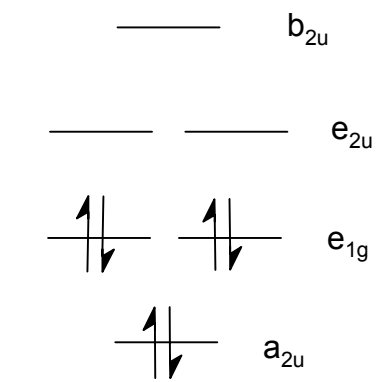
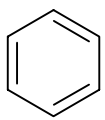
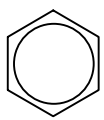
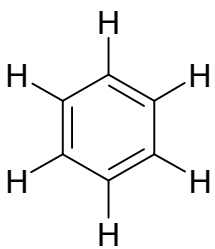
- Trivial name
  - Simple structures
  - Language dependant
- Systematic name
  - Complex molecules can be difficult to name
  - Often not unique
- Classification Systems
  - Beilstein
  - Derwent
- Graphical Structure
  - Universally understood by chemists

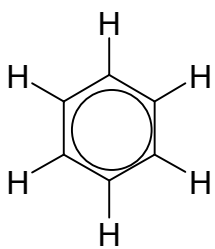
What is Benzene?









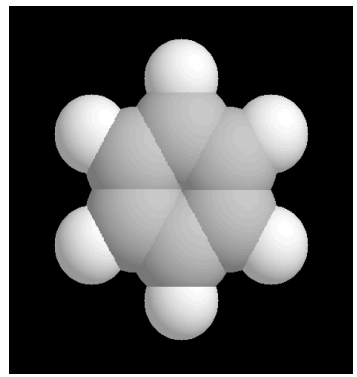


Connection table:

```
Benzene
 -ISIS-  08200115272D

  6  6  0  0  0  0  0  0  0  0999 V2000
   -1.0306   -1.4375    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
        0
   -1.0318   -2.2648    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
        0
   -0.3169   -2.6777    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
        0
    0.3995   -2.2644    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
        0
    0.3966   -1.4338    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
        0
   -0.3187   -1.0247    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
        0
  1  2  2  0  0  0  0
  3  4  2  0  0  0  0
  4  5  1  0  0  0  0
  2  3  1  0  0  0  0
  5  6  2  0  0  0  0
  6  1  1  0  0  0  0
M  END
```

Benzene



ID #: MUSE00000002

CAS #: 71-43-2

Line notation

- •Wiswesser: RH
- •MDL LN: C-C=C-C=C-C=@1
- •SMILES: c1ccccc1

Clear, colorless liquid with characteristic aromatic odor.

Formula: C_6H_6; Mol. Mass: 78.11184;

M.Pt: 5.512-5.544ºC; B.Pt: 80.11 ºC

Graphical Representation

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- Well understood by chemists
- Formalizes the molecule in terms of atoms and bonds
  - Based on atoms with a defined valency connected by bonds
  - Very powerful, but an approximation
- Started simple but flexibility needed
  - Variable valency, Bond types, Bond order
  - Organometallics
  - Hydrogen!
- Isomers
  - Geometric, optical, tautomers
- Isotopic variations
- Predates MO theory

Encoding: Perceive and Store

- Create special atom and bond types as necessary
  - Bond types
    - Tautomer bond
    - Aromatic
    - Cyclic / Acyclic
  - Atom types
    - Chiral center – R / S
    - Trigonal bipyramidyl atom
- Risky
  - Editing structure for new entity or sub-structure query may give incorrect answers
- Use for basic objects
  - Atoms in the periodic table: C / H / O / N / S / Cl / F / Br etc
  - Simple bond types: single / double / triple

Encoding: Store and Perceive

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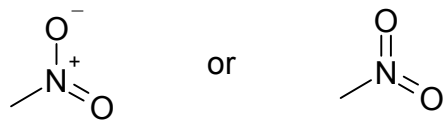
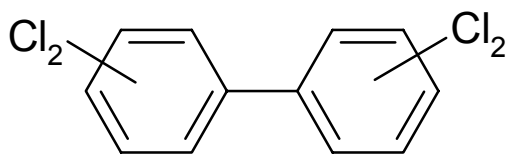
- Interpret atom environment and bond types at search time
  - Bond types
    - Tautomer bond
    - Aromatic
    - Cyclic / Acyclic
  - Atom types
    - Chiral center – R / S
    - Coordination number of atom
- Enhanced interpretations can be added without invalidating existing data
  - Upgrading (large) databases is undesirable
- Simplify structural input
- Structural business rules may simplify process

Graphical Representation

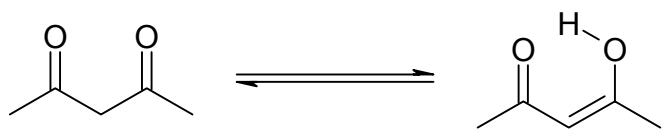
- Single entity may have more than one valid representation



- Chemists have learned to interpret the graphical representation



- More difficult for computer systems to interpret representations



Chemical structure business rules

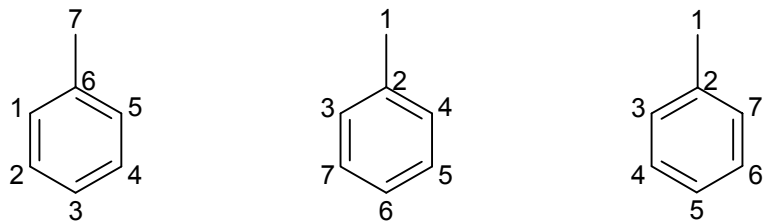
- Now widely adopted at the corporate level
- Standardize on one representation
  - enforce it a registration
  - Train users in the standardized representation
- Incorporate the business rules in the searching application

Flexible searches

- Incorporate search capabilities that introduce flexibility in the query
  - Similarity searching
    - Very flexible
  - MDL's Flexmatch operator
    - Encode basic structural connectivity
    - Add layers of constraints
      - Parent / Salt
      - Tautomer
      - Isotopic variations
  - Tend to be specialist capabilities

Retrieval

- Representation is only one part of the problem
- The query must be matched to the database entry
  - Methylbenzene
    - Examples:



  - Atom numbering depends on drawing history

Retrieval

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- Approaches
  - Select one form for storage and standardize the query
    - Canonical Approach
    - Rendered structure may have unusual orientation
  - Register any layout and build intelligence into the search engine
    - Most flexible
    - Preferred orientation is rendered

Sub-Structure Searching

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- Substructure searching (SSS) is a mature and well understood operation
  - Accuracy depends on quality of the search operation
    - Hits are expected
  - Value of the search depends on the richness of query properties available
    - Hits contain features of interest
  - Query properties are based on perception
    - Bond type: aromatic / any / cyclic / acyclic / etc
    - Ring bond count / substitution count
    - Atom lists; [O,S] / [Cl,Br,I]
    - Chiral centers; R / S
- Structure conventions are of value

What is Exact?

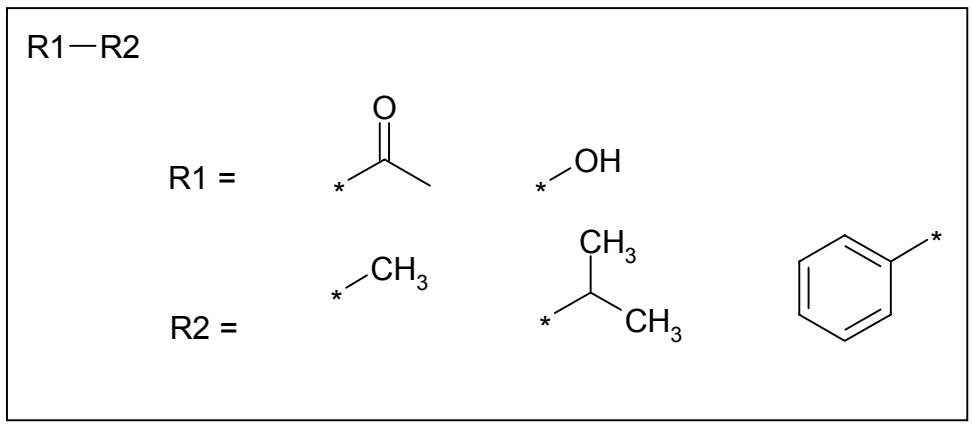
- Exact match can be problematic
  - Structure conventions for registration and queries are beneficial
    - Nitro group
  - Provide a tunable search operator
    - MDL's Flexmatch search
      - tautomer
      - Parent
      - Isotopic variations

Searching technology

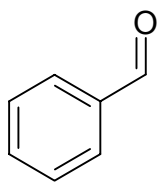
- Modern tree-based indexing technologies provide excellent performance for large databases
- Key-based indexing is limited for modern database sizes
  - Secondary benefit: modal fingerprint applications
- Hash-based indexing for canonical features
  - Flexmatch keys

Generic structures

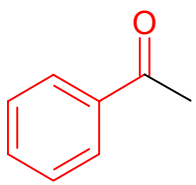
- Must be able to map query over root-Rgroup boundary
  - Database entry:



  - Query



  - Hit



Stereochemical representation

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- Remains a major problem for both representation, encoding and searching
- Pure samples that contain only absolute or relative centers can be named and characterized
- This is not reality
  - Chiral centers are seldom optically pure
  - Samples with both absolute and relative centers are common

Tracking stereochemistry of samples

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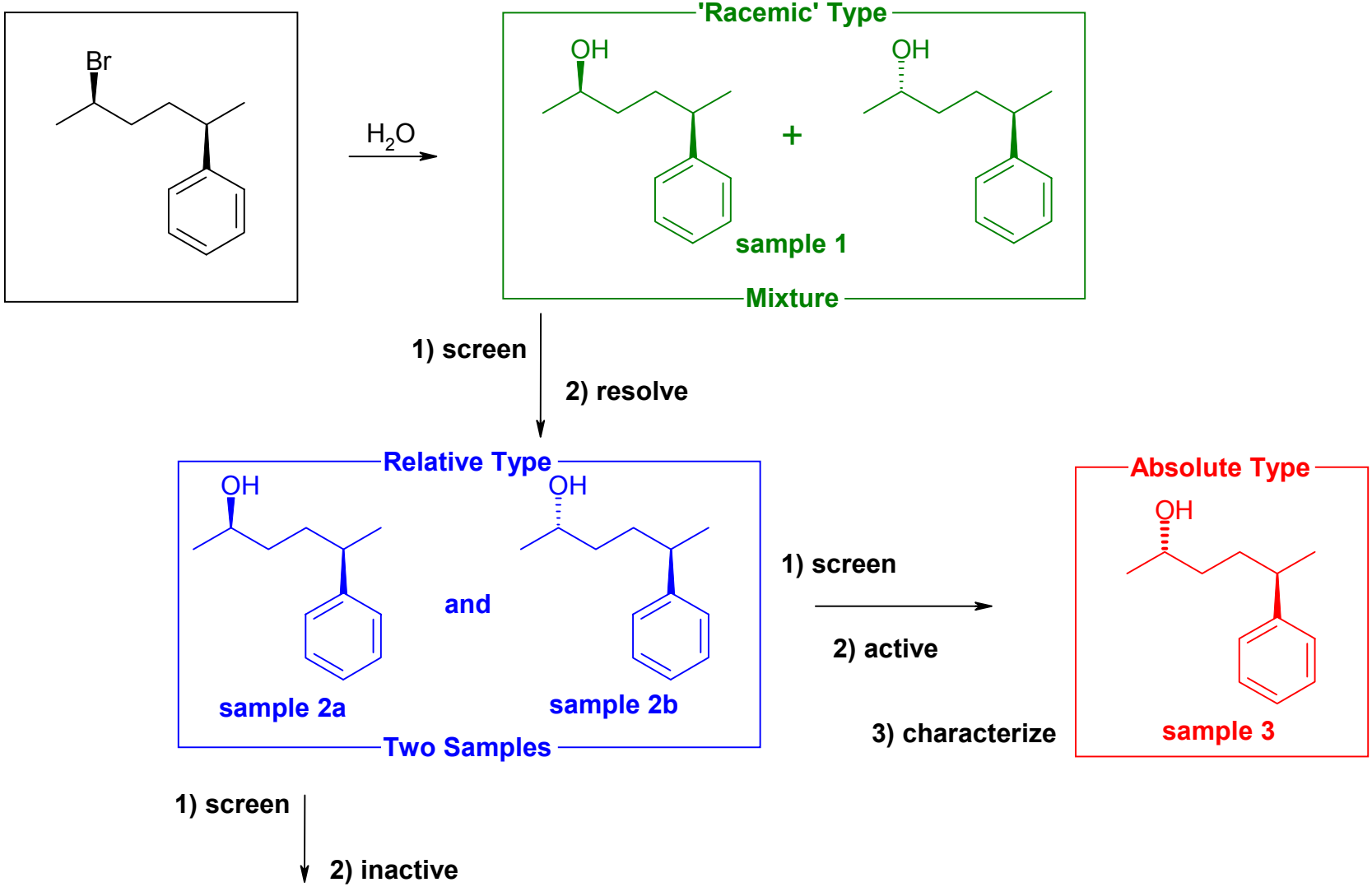
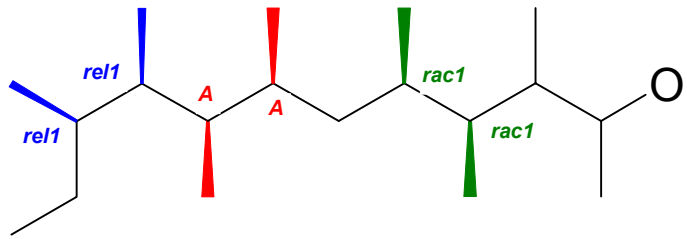
- Traditionally stereochemical qualifiers are stored separately from the structure
  - Embedded in structure's name
  - Stored in a separate field in the database
  - Information is easily lost or corrupted
- Need to track all the stereochemical information and associate it with properties (activity)

A high throughput synthesis workflow

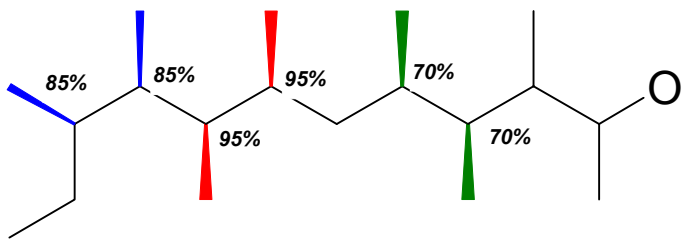


Typical samples

- Contain a combination of types:



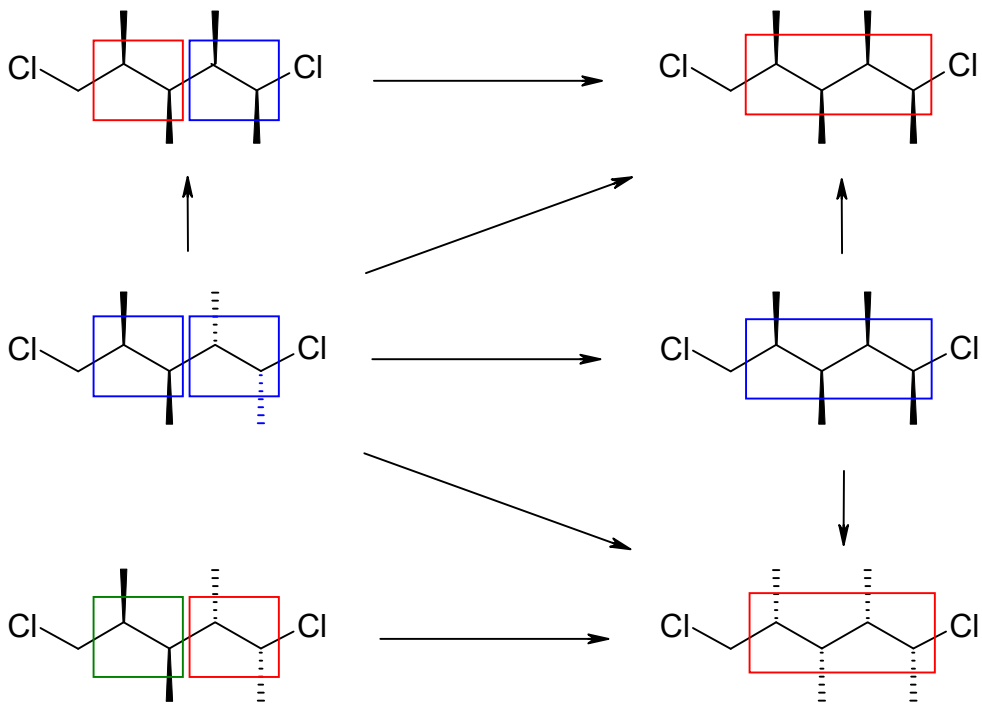
- And purity information is needed



Retrieval

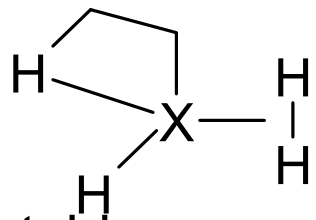
- All potentially valid hits are shown

Absolute
Relative
'Racemic'



Summary

- Chemical database technology well developed
- Representations are rich but not complete
  - Organometallics and transition metal complexes
  - And hydrogens



- Registration without matching representation is of little value
- Registration without retrieval is of little value
- User Interfaces are the key to acceptance
  - Personal preferences for structure representation
  - Use appropriate representation