Modelling of Stereoisomerism for Generative Chemistries

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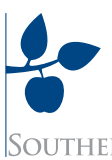
Bled, February 2015



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A Note on Terminology

External Representation

The external storage format used for data exchange.

(E.g., a molecule is stored as a SMILES string, or InChI string)

Internal Representation (Implementation)

The data structures used to represent the the model, and the algorithms to manipulate the data.

(E.g., a molecule is an adjacency list with . . .)

Model

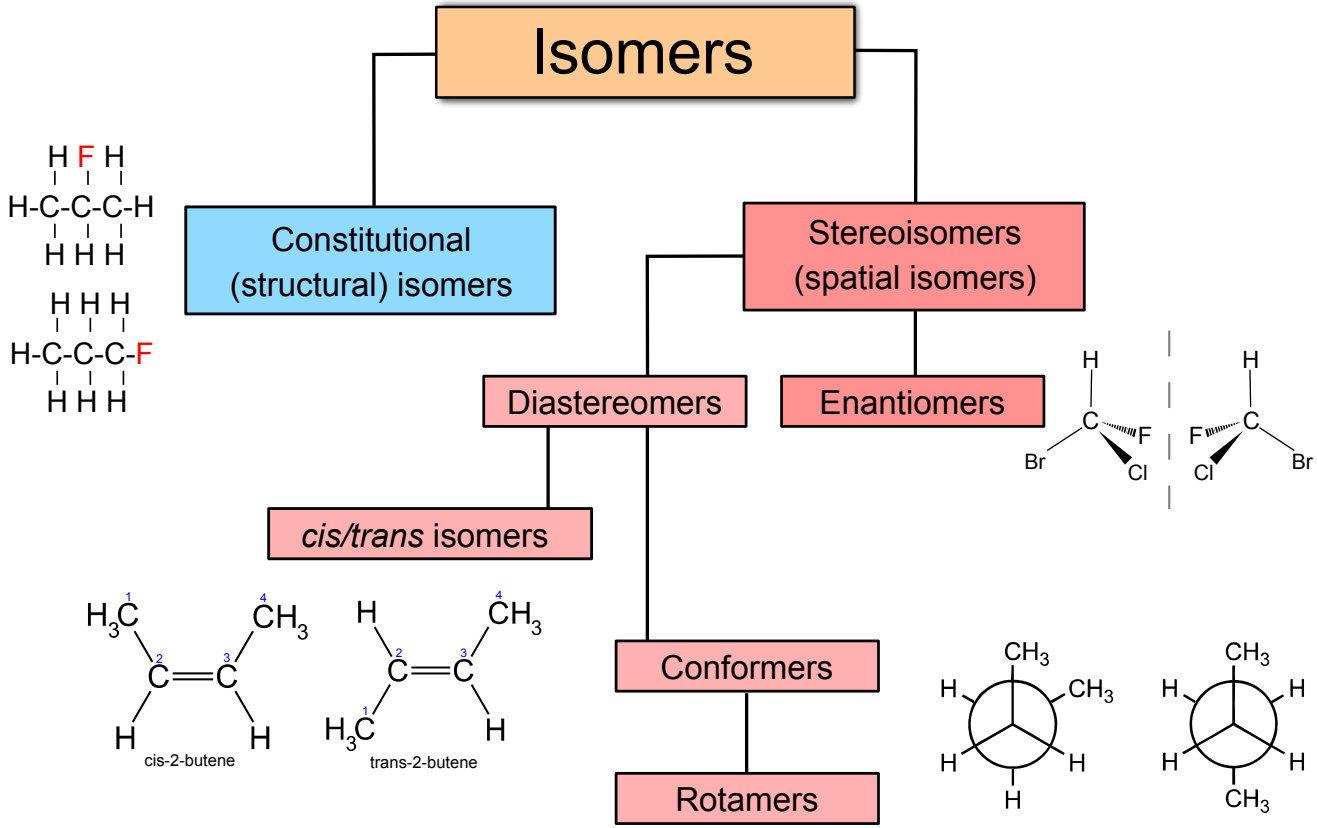
The abstract mathematical description of objects and their semantics.

(E.g., a molecule is an connected, undirected, simple, labelled graph.)

Reality

???

Isomers

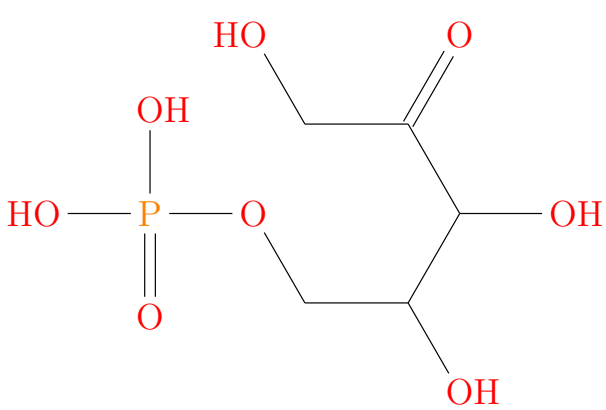


"Isomers are molecules with the same chemical formula but different chemical structures." [Wikipedia, Isomer]

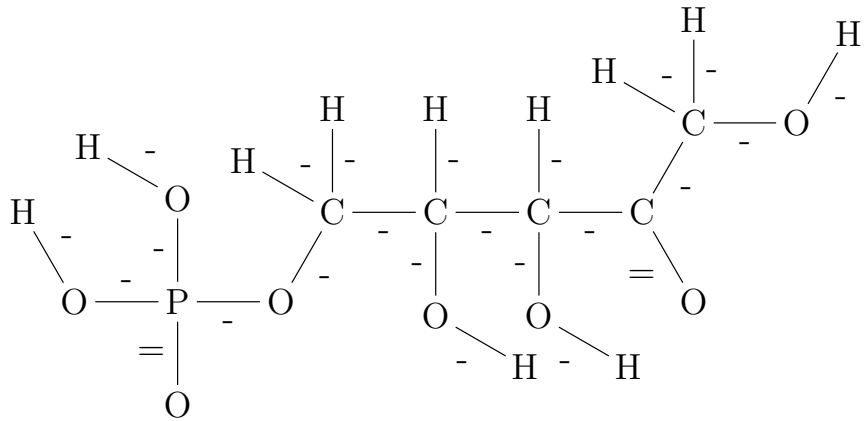
(not to be confused with the "structure" in "structural isomers")

Our Current Molecule Model

A molecule is a connected, undirected, simple, labelled graph.



(a) A molecule

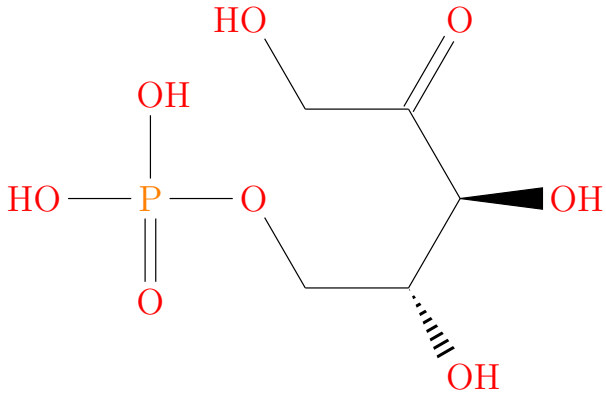


(b) A model of a molecule

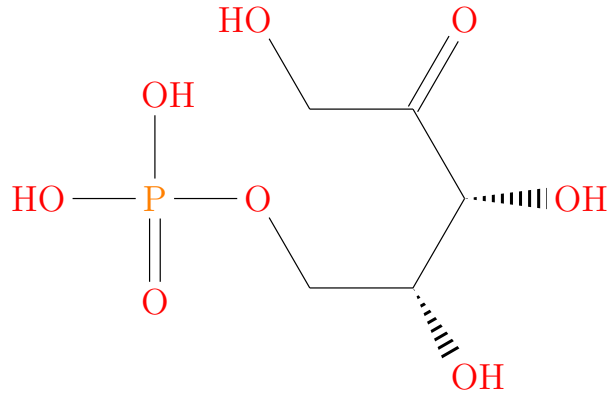
We can distinguish between constitutional (structural) isomers. . .

Our Current Molecule Model

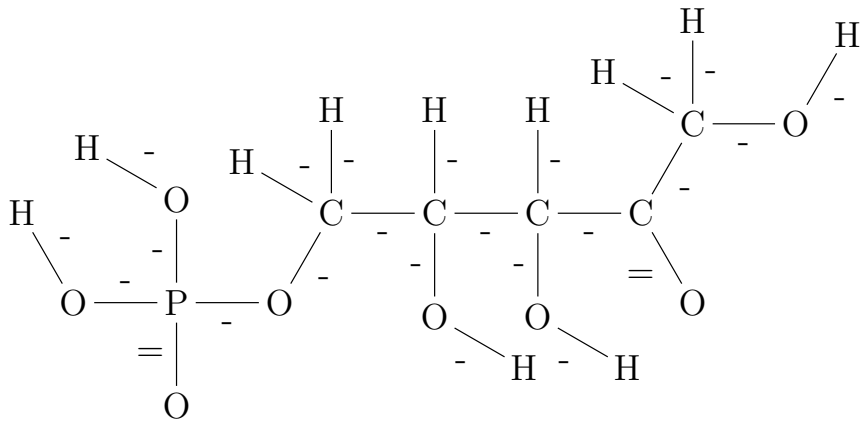
. . . but not stereoisomers.



(a) Ribulose 5-phosphate



(b) Xylulose 5-phosphate



(c) The model for both molecules.

Our Current Molecule Model

Data Structures

- Graphs with labels (adjacency lists with strings).

  Only local information about atoms and bonds.

Algorithms

- Graph isomorphism

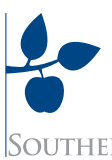
  Are two data structures representations of the same graph?
- Subgraph monomorphism

  Pattern matching for graphs. Substructure search.
- Composition of transformation rules

  Generalised graph transformation. Computing reactions.
- Graph canonicalisation

  Faster isomorphism check. Making "comfortable" storage formats.

We would like to model stereochemistry as well.



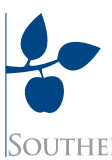
Extension for Modelling (Some) Stereochemistry

Goals

- Molecules are still graphs, but now with more information.
- Information is still localised on atoms and bonds.
- It should really be an extension: the current algorithms are simplifications of the new algorithms.

Limitation

- Only local geometry (or derived thereof) can be modelled.



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Data Structures

- Each edge (bond): A *behaviour* (usually the bond type)
- Each vertex (atom):
  - Number of incident lone pairs.
  - A geometry tag.
  - An ordered list of incident edges and lone pairs.

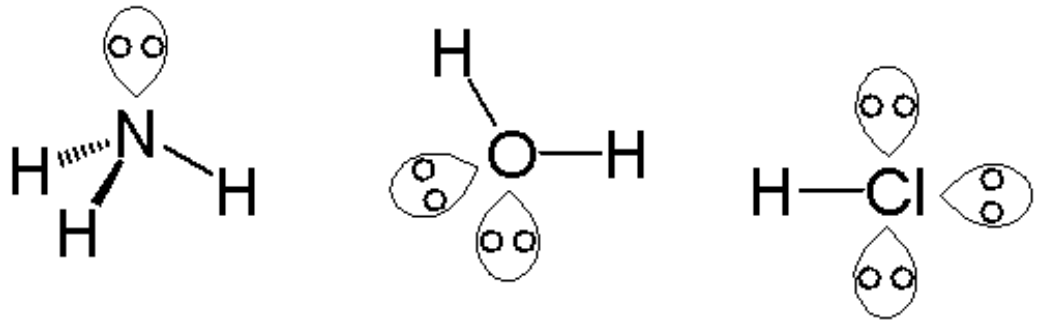
Based on "the ordered list method".

[Petrarca et al., J. Chem. Doc., 1967]

[Wipke and Dyott, J. Am. Chem. Soc., 1974]

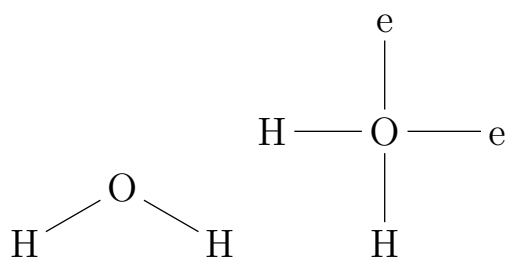
Lone Pair-Augmentation

Lone pairs contribute to the geometry.



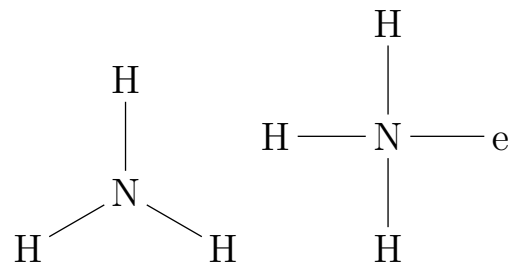
[Wikipedia, Lone Pair]

Add a virtual edge and vertex for each lone pair:



(a) Before (b) After

Oxygen in water.



(a) Before (b) After

Nitrogen in ammonia.

(A virtual edge has single bond behaviour as default.)

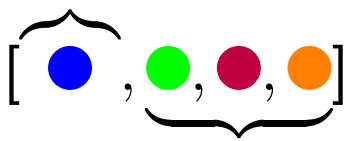
Example: TetrahedralFree

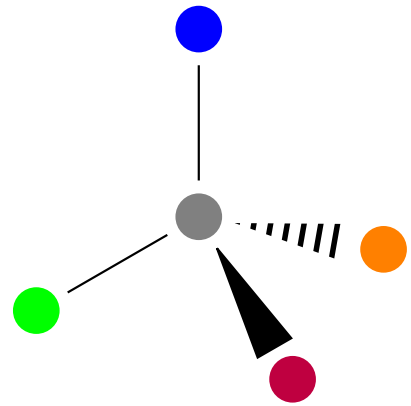
Tetrahedral $\equiv$ 4 neighbours, tetrahedron shape

Free $\equiv$ all have single bond behaviour

(E.g., a carbon with 4 bonds)

Ordering Semantics





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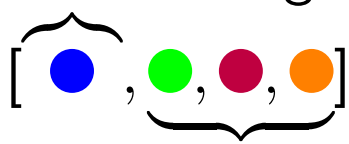
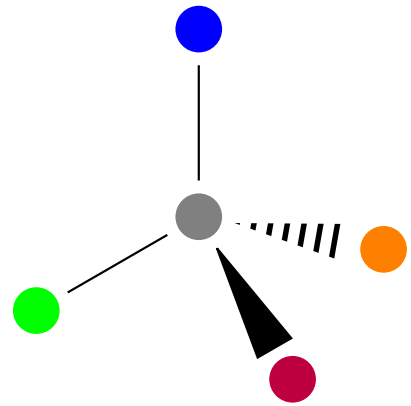
Ordering Semantics

"up" is where hte first neighbour points





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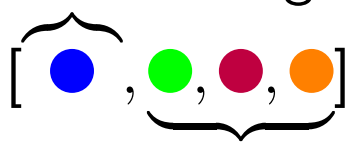
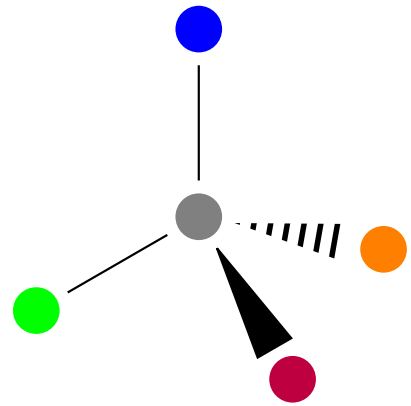


in positive order from above



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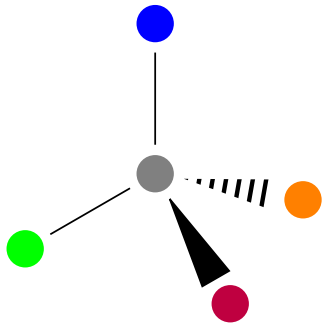
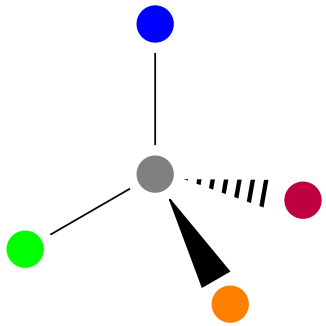
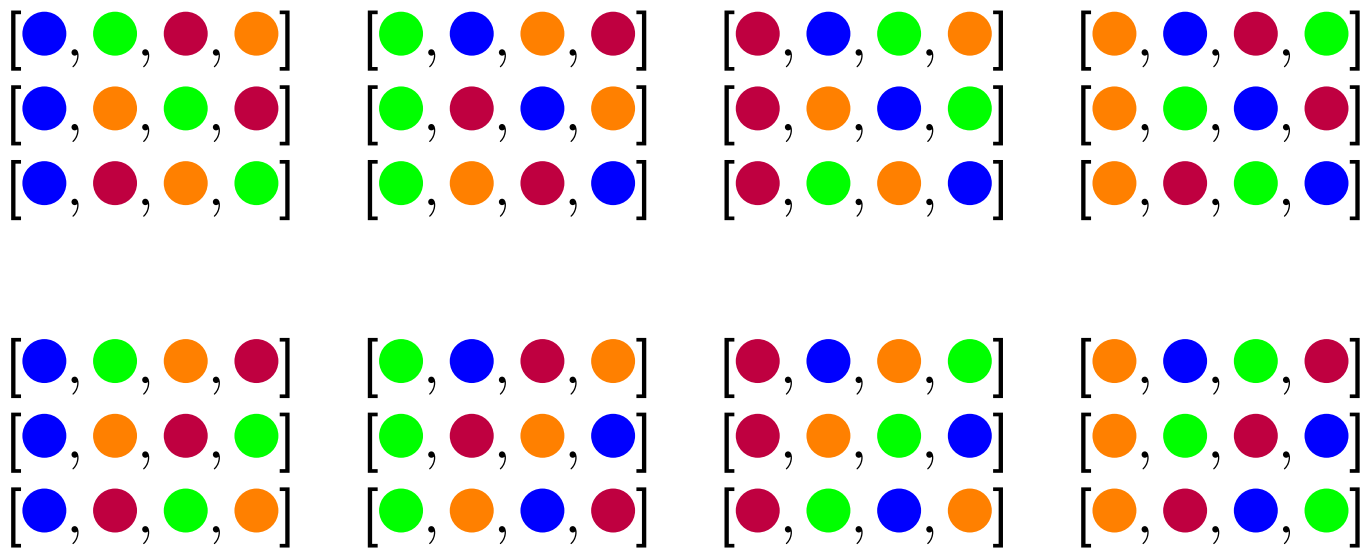






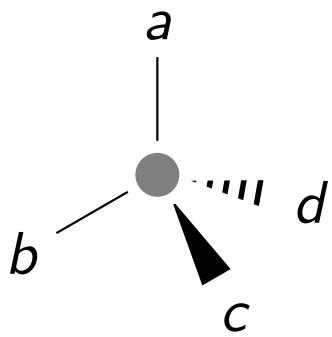
Equivalence permutation group: $G_{\equiv} = \langle (1)(2\ 3\ 4), (1\ 2)(3\ 4) \rangle$

Non-equivalence permutations: $G_{\not\equiv} = G_{\equiv} \circ (1)(2)(3\ 4)$

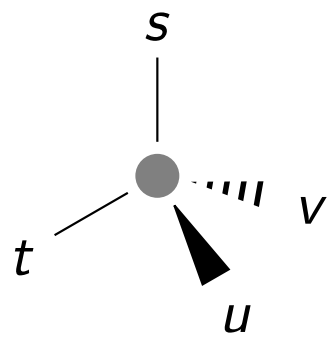
Example: TetrahedralFree, Isomorphism

Given a graph isomorphism.

Decide if it is still valid with stereo information.



$[a, b, c, d]$



$[s, t, u, v]$

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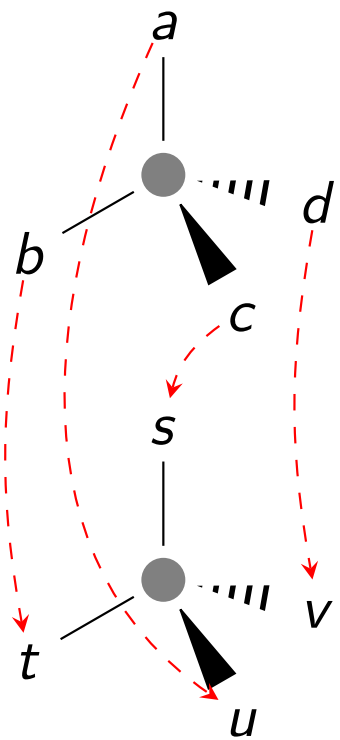

$[a, b, c, d]$

Induced permutation: (1 3)(2)(4)

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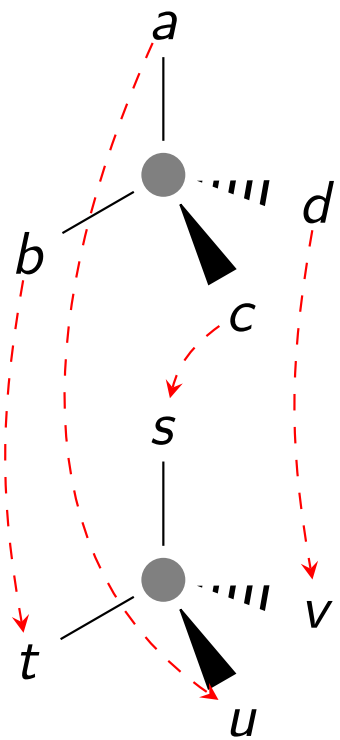


$[a, b, c, d]$

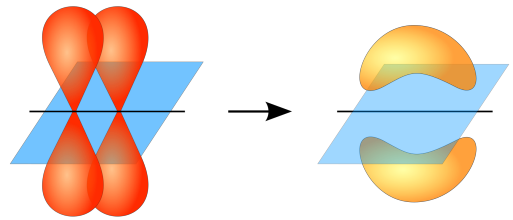
Induced permutation: $(1\ 3)(2)(4) \in G_{\not\equiv}$

$[s, t, u, v]$

Edge Behaviours (Bond Types)

- SINGLE: no rotational constraints.
- DOUBLE: inhibits rotation, 1 reference half-plane.

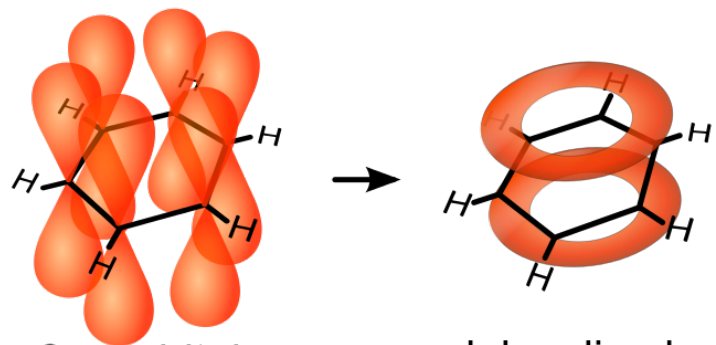
Formation of π-bond:



[Wikipedia, Pi bond]

- TRIPLE: inhibits rotation, 2 reference half-planes.
- CONJUGATED: inhibits rotation, 1 reference half-plane.

Formation of conjugated bonds:



[Wikipedia, Conjugated system]

Example: TrigonalD

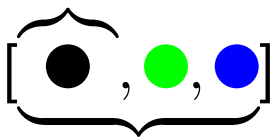
TRIGONAL $\equiv$ 3 neighbours, planar shape

D $\equiv$ 1 double bond, 2 single bonds

Ordering Semantics

The ordering defines a reference half-plane.

always the double bond



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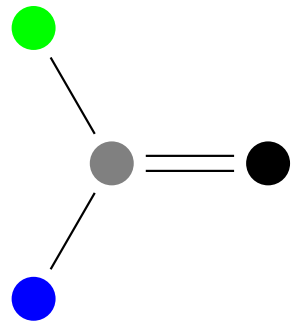
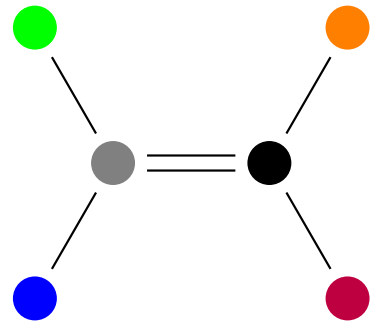


- Incident reference half-planes are equal.
- [●, ●, ●] and [●, ●, ●] have opposite half-planes.
  Half-plane-swapping permutation(s): $G_{\circlearrowleft} = \{(1)(2\ 3)\}$.
- $G_{\equiv} = \{(1)(2)(3)(4)\}$, $G_{\not\equiv} = \emptyset$

Example: TrigonalD

Either ●: [●, ●, ●] ●: [●, ●, ●]

or ●: [●, ●, ●] ●: [●, ●, ●]



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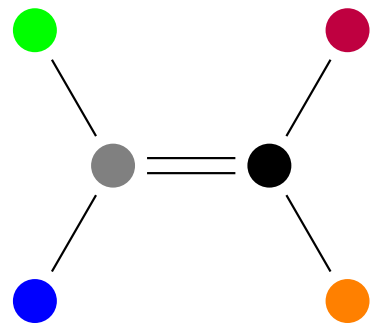

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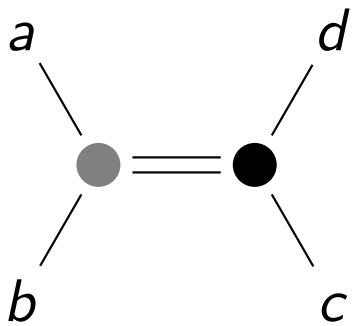
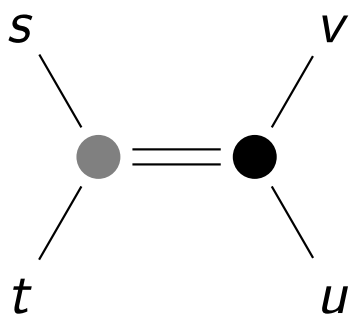
Decide if it is still valid with stereo information.



●: [●, a, b] ●: [●, c, d]



●: [●, s, t] ●: [●, u, v]

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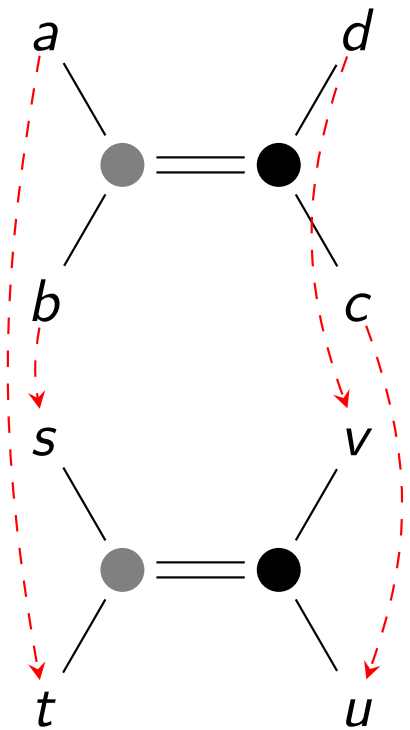

●: [●, a, b] ●: [●, c, d]

Induced permutations:

●: (1)(2 3) ●: (1)(2)(3)

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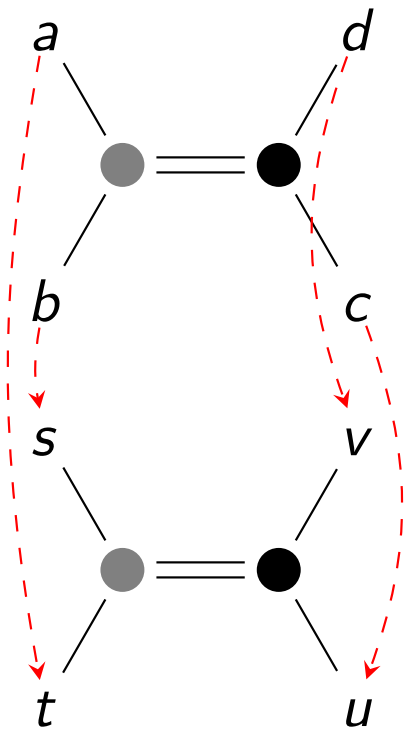

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●: $[●, s, t]$ ●: $[●, u, v]$

● swaps half-plane, ● does not ⇒ invalid isomorphism.

Example: LINEARDD

LINEAR $\equiv$ 2 neighbours, linear shape

DD $\equiv$ 2 double bonds

Ordering Semantics

The ordering does not matter:

[●, ●] and [●, ●] mean the same.

I.e., $G_{\equiv} = \langle (1\ 2) \rangle$

Half-plane Propagation

The other half-plane is at 90°, seen from either end.

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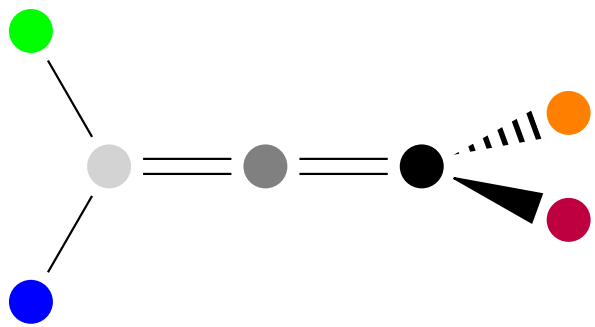
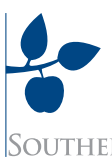


(Partially) Unspecified Stereo Information

- Our current molecules have no information.
  (absence of information $\equiv$ completely unspecified information)
- Parts of a molecule may have unspecified information.
- Part of a local configuration may be unspecified
  (e.g., in trigonal bipyramidal geometry).



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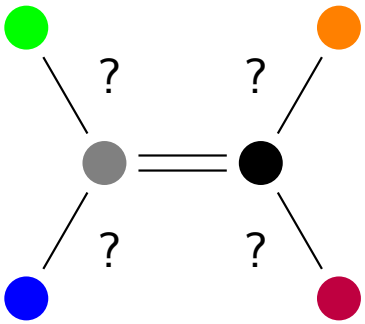
Data Structure

- Attach a "fixed"-flag to each ordering element.
  (they may not be mutually independent)

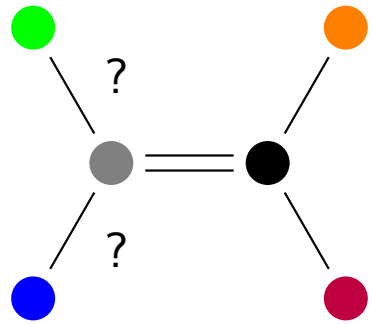
Semantics

- Fixed elements may still be moved by $G_{\equiv}$.
- Moves permutations with the non-stabilised elements all being non-fixed into $G_{\equiv}$.
- Variations of the same molecule are now partially ordered by generality/specificity.

(Partially) Unspecified Stereo Information



is less (specific) than
is not isomorphic to
can unify with



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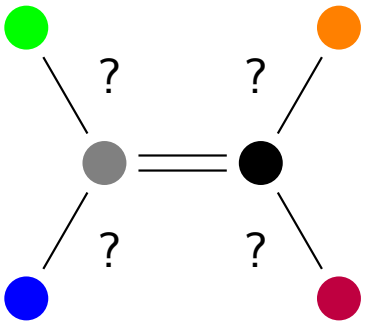

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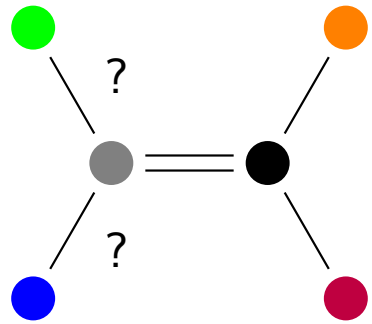
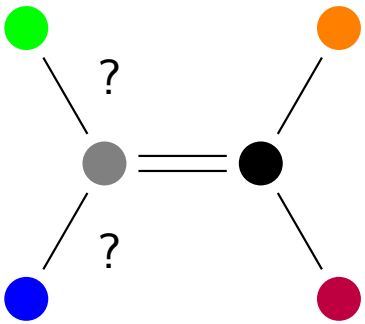
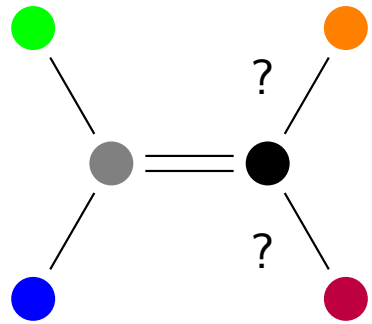
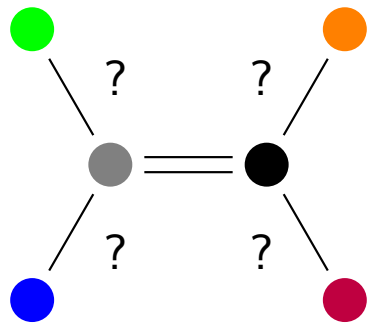




is incomparable (by specificity) to
is not isomorphic to
can unify with



Partial Order of Graphs (Specificity)



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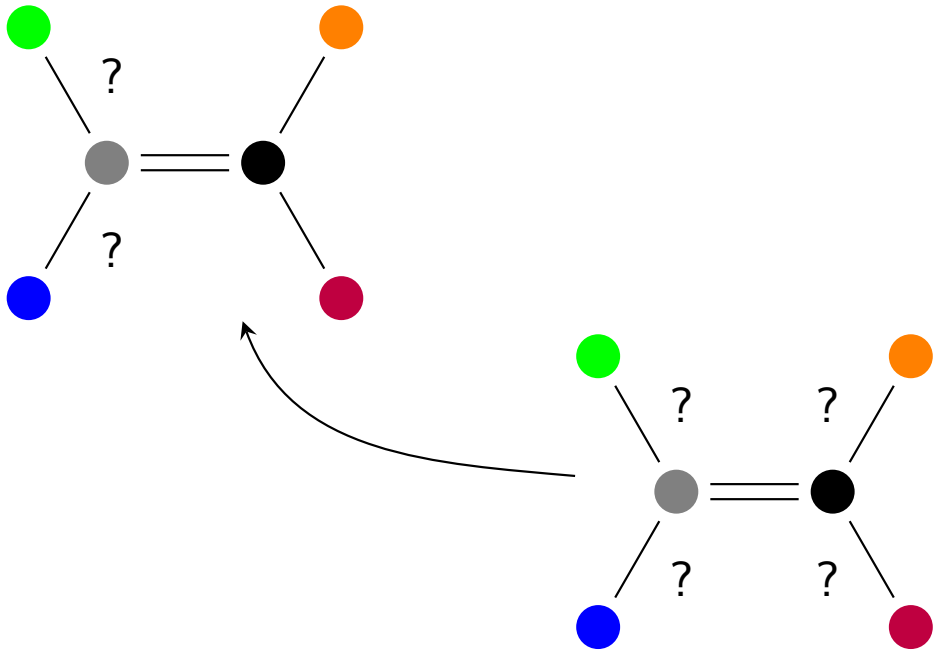

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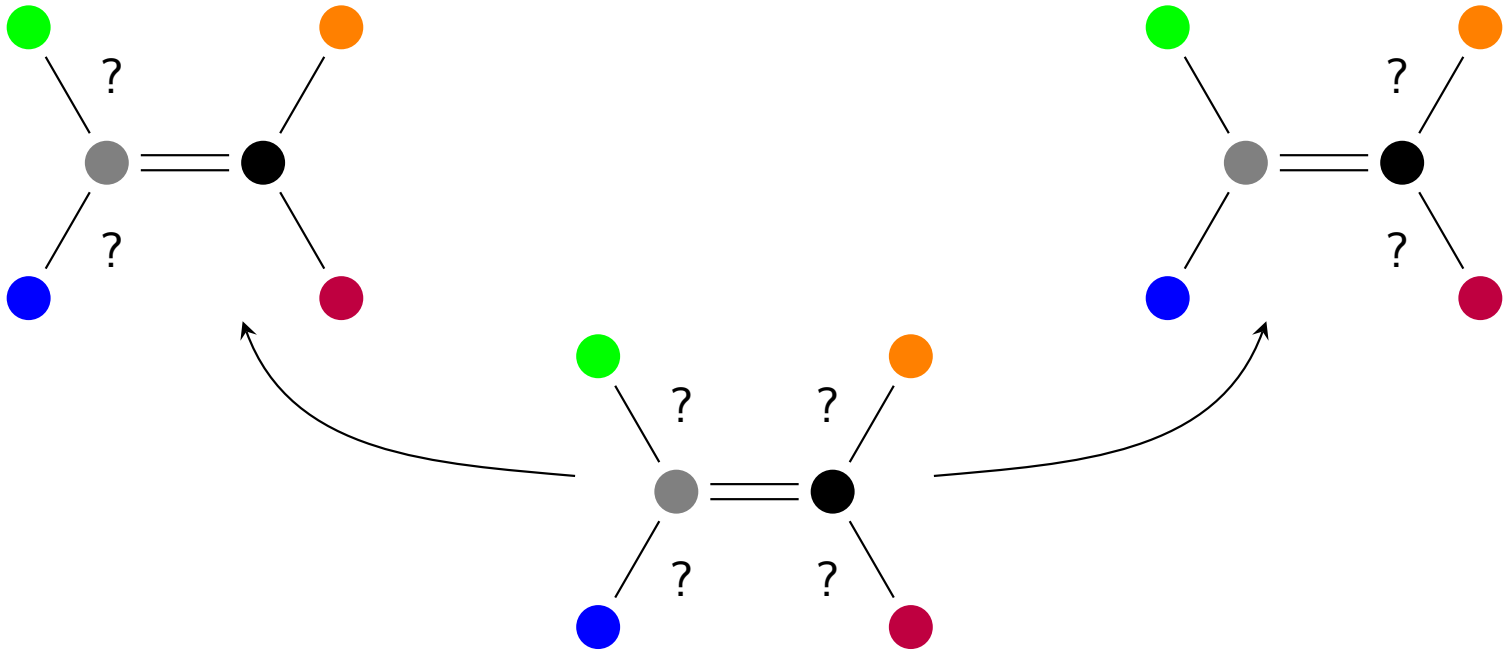

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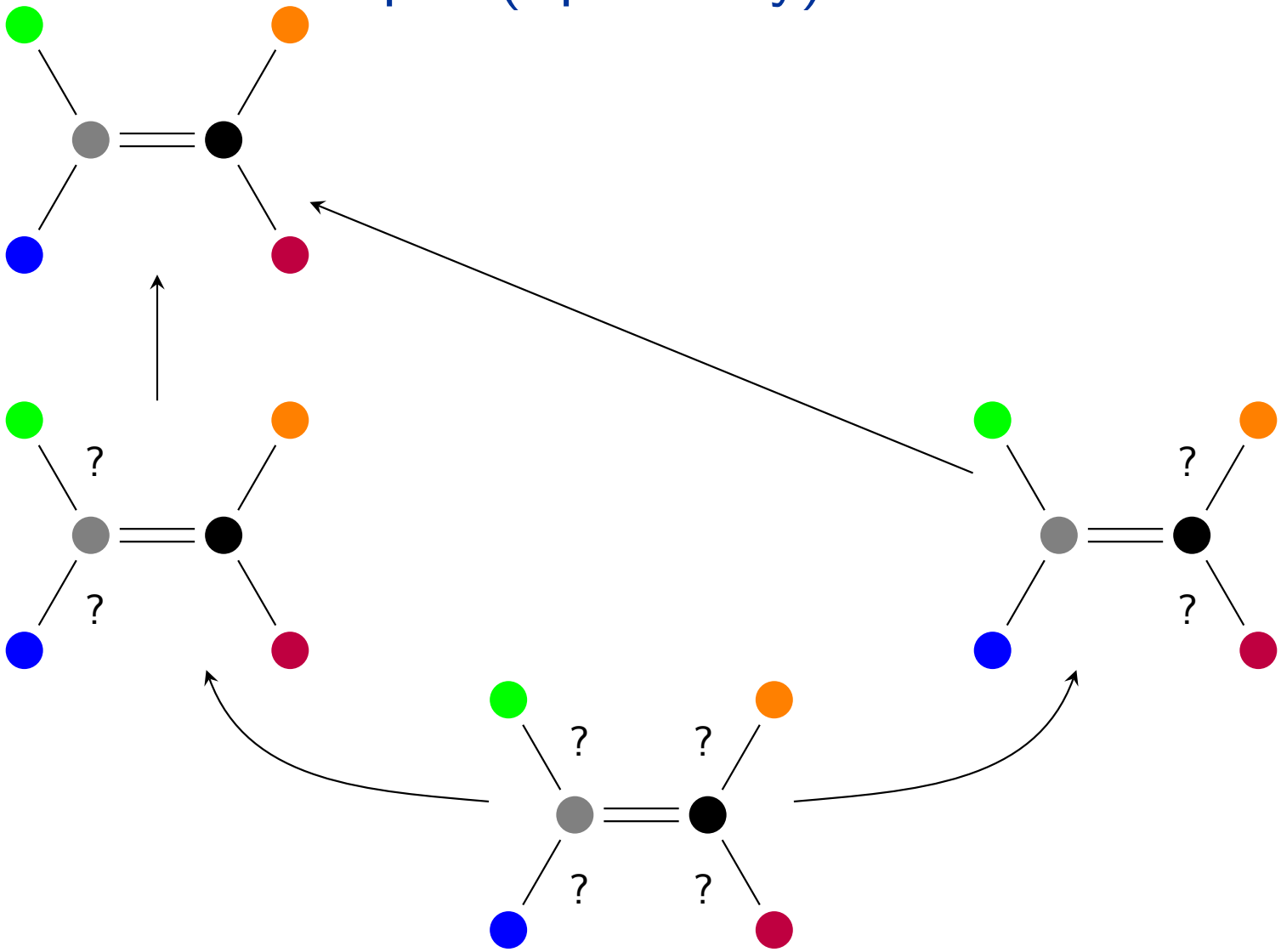

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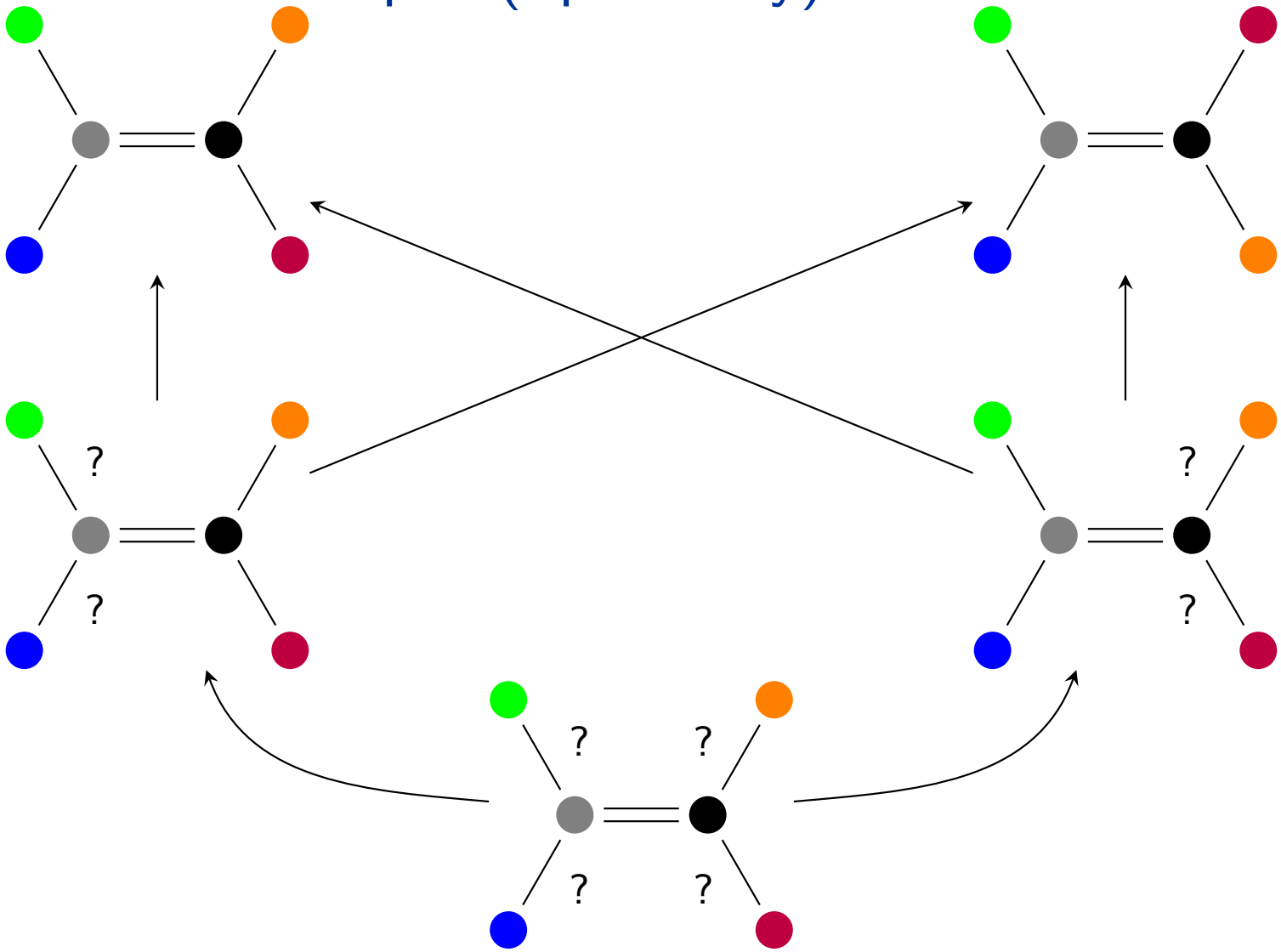

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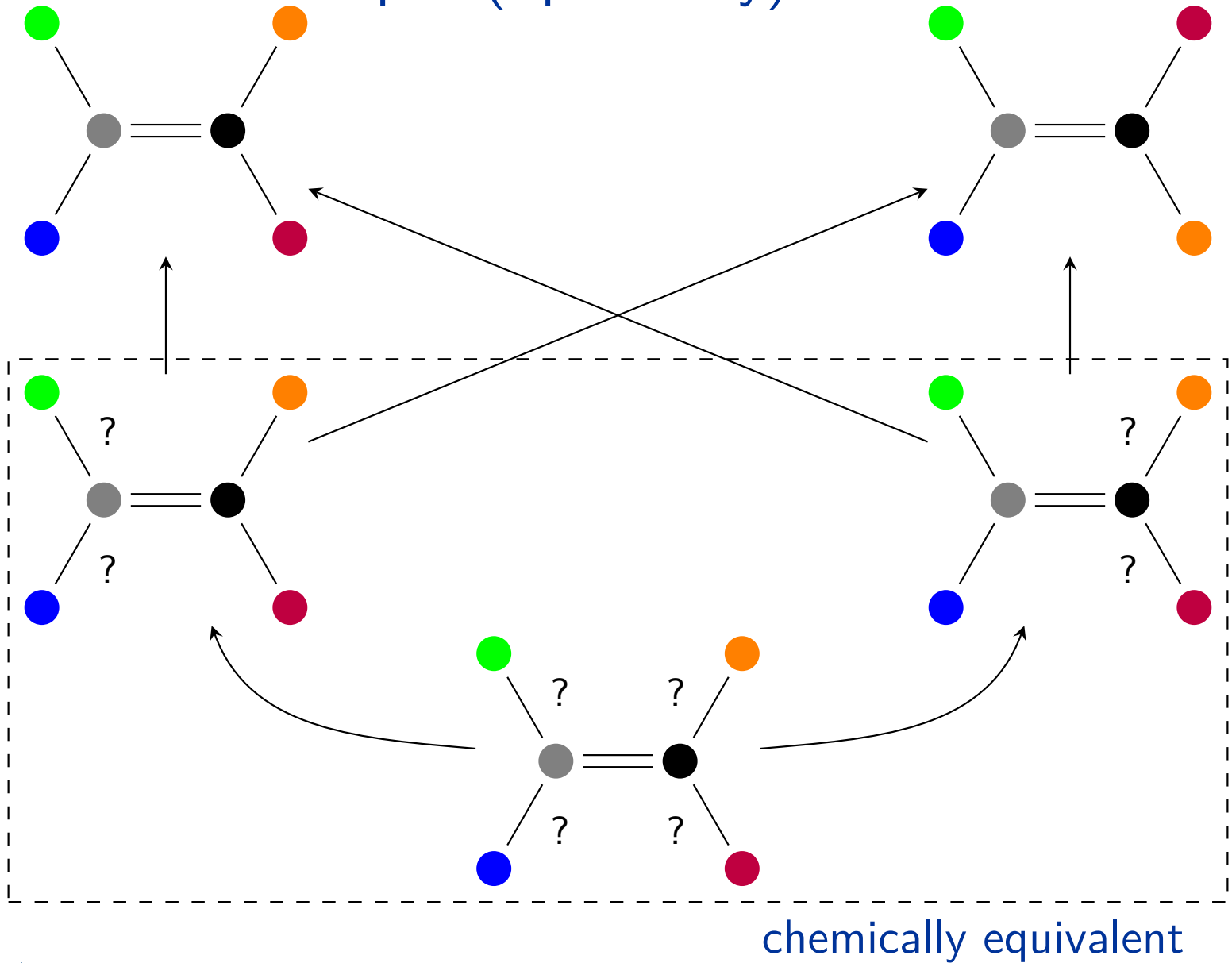


Substructures with Stereo Information

Modelling status

- In progress.

Some thoughts

- Partially specified geometries (encoding of "I don't care").
- Partially specified orderings ("virtual neighbours").
- Transformation rules that change stereo information.
- Transformation rules that fix/relax stereo orderings.
- Heavy use of variations of techniques from term rewriting.

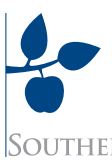
Some time in the future...

```
rule [  ruleID "Stereospecific Diels-Alder"
left [
    node [ id 1 label "C" stereo [ order "2, -_b, -_a" ] ]
    node [ id 4 label "C" stereo [ order "3, -_d, -_c" ] ]
    edge [ source 1 target 2 label "=" ]
    edge [ source 2 target 3 label "-" ]
    edge [ source 3 target 4 label "=" ]

    node [ id 5 label "C" stereo [ order "6, -_f, -_e" ] ]
    node [ id 6 label "C" stereo [ order "5, -_g, -_h" ] ]
    edge [ source 5 target 6 label "=" ]
]
context [
    ndoe [ id 2 label "C" stereo [ order "1, -, 3" ]  ]
    ndoe [ id 3 label "C" stereo [ order "4, 2, -" ]  ]
]
right [
    node [ id 1 label "C" stereo [ order "2, 5, -_a, -_b" ] ]
    node [ id 4 label "C" stereo [ order "3, 6, -_c, -_d" ] ]
    node [ id 5 label "C" stereo [ order "6, 1, -_e, -_f" ] ]
    node [ id 6 label "C" stereo [ order "5, 4, -_h, -_g" ] ]
    edge [ source 1 target 2 label "-" ]
    edge [ source 2 target 3 label "=" ]
    edge [ source 3 target 4 label "-" ]
    edge [ source 4 target 5 label "-" ]
    edge [ source 5 target 6 label "-" ]
    edge [ source 6 target 1 label "-" ]
]   ]
```

Summary and Current Status

- Modelling of stereochemistry is non-trivial.
- A lot of fun algorithmics.
- It seems is doable, using only local properties.



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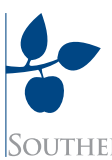

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Subset of related challenges

- Canonicalisation algorithm (in progress).
- Deciding if something is a valid molecule.
- Visualisation in 2D and 3D.
- Inference from input (R/S, E/Z, . . .).
- Interconversion with SMILES (whatever that is).
- Interconversion with the “open” “standard” InChI.

Thank You for Listening

"Fortunately, the charging one has been solved now that we've all standardized on mini-USB. Or is it micro-USB? Shit."

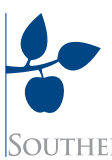
[XKCD: Standards]

Bonus Slide: SMILES

- The original version is proprietary, but OpenSMILES exist.
- Unclear/unfinished specification.
- Missing/unclear molecule model.
- No true support for conjugated bonds.
- Everyone seems to implement their own specification.
- Widespread belief that “the canonicalisation algorithm” works. (hint: it doesn’t)

Bonus Slide: InChI

- "IUPAC International Chemical Identifier"
- Identity crisis: is it a standard, tool, or algorithm?
- Missing/unclear molecule model.
- No separation between standard/specification and implementation.



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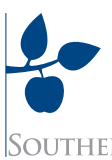

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-
```
if ( k < r ) {
    goto L9; /* cannot understand it... */
}
```

[InChI source code, the canonicalisation code]