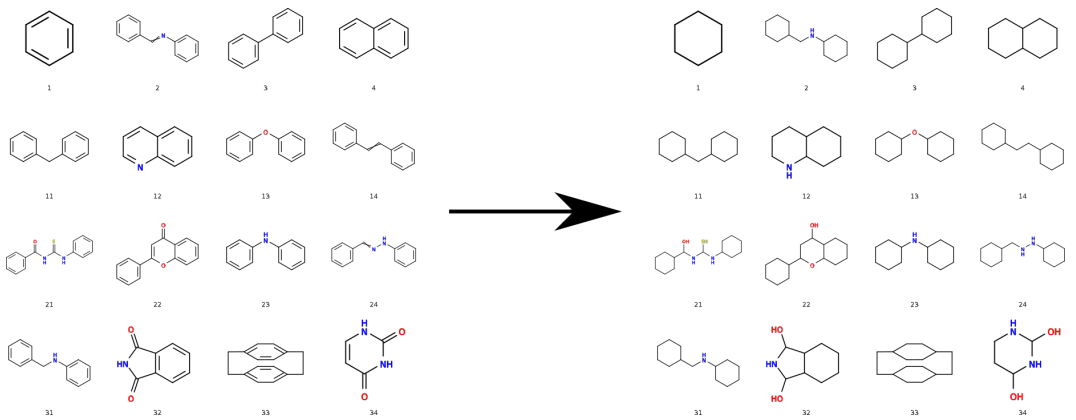
1 Background

The Bemis-Murcko scaffold[1] provided by DataWarrior[2] retains information about bond order and chirality. Sometimes, however, it suffices to retain only atom connectivity, like an assumption «there are only single bonds». Note, DataWarrior equally offers the export of Bemis-Murcko skeleton, however this simplifies e.g. the scaffold about an imidazole into one of cyclopentane.



2 Typical use

After the installation (see below), the script's general input follows the pattern of

```
saturate_murcko_scaffolds [-h] inputs [inputs ...]
```

Running from the CLI, this translates for example the SMILES strings about pyridine and benzene to the ones about piperidine and cyclohexane

```
$ saturate_murcko_scaffolds c1ccncc1 c1ccccc1
C1CCNCC1
C1CCCCC1
```

It equally is possible to provide the input as a list of SMILES in a text file. As an example run in Linux Debian 13:

```
$ cat test.smi
c1ccncc1
c1ccccc1
```

[1] Bemis, G. W.; Murcko, M. A. The Properties of Known Drugs. 1. Molecular Frameworks. *J. Med. Chem.* **1996**, *39*, 2887–2893 (https://doi.org/10.1021/jm9602928).

[2] Sander, T.; Freyss, J.; Von Korff, M.; Rufener, C. DataWarrior: An Open-Source Program For Chemistry Aware Data Visualization And Analysis. *J. Chem. Inf. Model.* **2015**, *55*, 460–473 (https://doi.org/10.1021/ci500588j). The program, (c) 2002–2024 by Idorsia Pharmaceuticals Ltd., is freely available under http://www.openmolecules.org. For the source code (GPLv3), see https://github.com/thsa/datawarrior.

```
$ saturate_murcko_scaffolds test.smi
C1CCNCC1
C1CCCCC1
```

In a mixed input queue, SMILES strings provided via the CLI are processed prior to SMILES provided via one, or multiple input file(s). If wanted, the output to the CLI can be redirected to (piped into) the input of the next command-line utility, or appended to an already existing permanent record, for instance

```
$ saturate_murcko_scaffolds test.smi > output.smi
$ cat output.smi
C1CCNCC1
C1CCCCC1
```

3 Installation

For normal use, download the most recent Python .whl enclosed in a zip archive distributed on the releases page. Within e.g., an activated virtual environment, the installation proceeds purely locally in the pattern of

```
pip install saturate_murcko_scaffolds-1.3.1-py3-none-any.whl
```

Intentionally, the Python script and subsequent .whl are set up to work regardless of the underlying operation system (Windows,[3] Linux, or MacOS) out of the box with the standard library of Python (version 3.10, or higher).

You equally can clone the GitHub repository to then proceed by either command of

```
pip install .
pip install .e
```

Note (because of `pip`) this requires a working connection to the internet during the installation.

If you are interested to locally edit and develop further the application, `pyproject.toml` lists additional tools like `flake8` and `pytest` distributed on the PyPI to check and improve source code quality. Then, the command

```
pip install pyproject.toml[dev]
```

resolves these dependencies. Finally, a GNU Makefile provides additional analytic tools.

[3] Contrasting to `cmd.exe`, Windows' PowerShell may block the execution of scripts. The later is adjustable by the command `set-executionpolicy remotesigned` while running in the administrator mode. For additional details, visit for instance How to enable execution of PowerShell scripts? on StackExchange/superuser.

4 Larger example

For a collection of organic materials, the Bemis-Murcko scaffolds were extracted with DataWarrior (then release 5.0.0 for Linux, January 2019) as listing `input.smi` including higher bond orders (see folder `demo`) with a redirect of the output into file `input_sat.smi`. The effect of the «artificial saturation» is easy to recognize while comparing the scaffold lists (fig. 1) in a difference view.

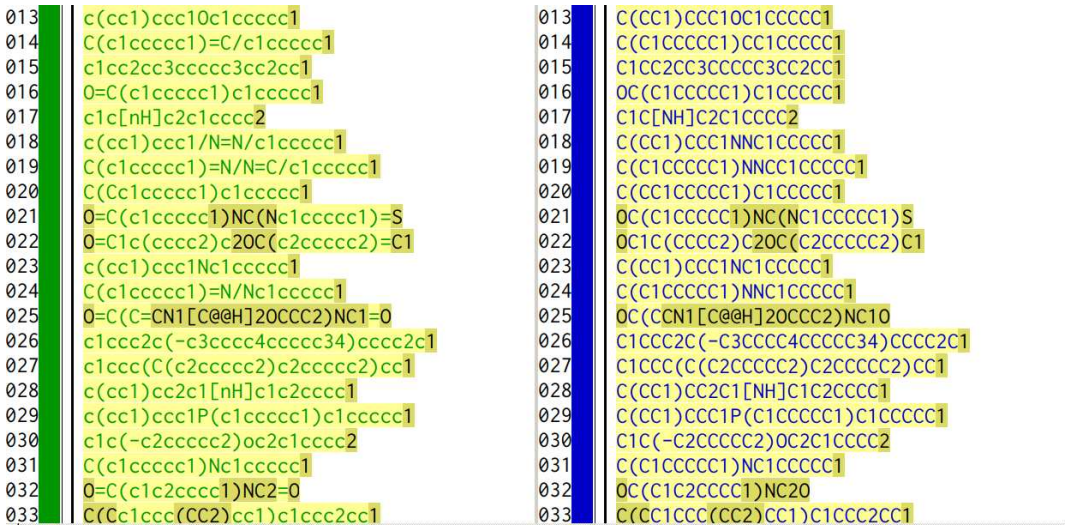


Figure 1: Difference view of the SMILES strings of a Murcko scaffold *prior* (left hand column) and *after* an «artificial saturation» (right hand column). The processing affects explicit bond order indicators, e.g. double bond (equality sign, e.g., line #14), triple bond bond (number sign #, not shown); or about implicit aromatization (lower case to upper case) for atoms of carbon, nitrogen, oxygen (depicted); or phosphorus, sulfur (not depicted). Stereochemical indicators about double bonds will be removed (e.g., slashes in lines #18 and #19). Descriptors of stereogenic centers (@-signs, e.g., line #25) and charges (not shown) are copied verbatim.

OpenBabel[4] is used to illustrate the work of the script. The instructions to the CLI follow the pattern of

```
obabel -ismi test_input.smi -O test_input_color.svg -xc10 -xr12 -xl --addinindex
```

to generate a `.svg` file (vector representation), or

```
obabel -ismi test_input_sat.smi -O test_input_sat_color.png -xc10 -xr12 -xl
↪  --addinindex -xp 3000
```

to generate a bitmap `.png` with structure formulae depicted in a grid of 10 columns by 12 rows. Script `series.py` automates the generation of the illustrations about both structure data sets.

It is remarkable how well OpenBabel's displays the molecular structures with advanced motifs. In addition to those shown in the first illustration of this guide, see sub-folder `test_data`

[4] https://github.com/openbabel/openbabel For the most recent documentation, see https://open-babel.readthedocs.io/en/latest/

for a more extensive survey (e.g., the scaffold of cyclophane [entry #33], sparteine [#38], or adamantane [#50]).

5 Known peculiarities

The script provides «saturation» by dropping explicit information related to double and triple bonds which SMILES encode (=, # regarding bond order; / (forward slash), \ (backward slash) regarding (*cis*)-(*trans*) relationship around double bonds). While processing double bonds of e.g., ketones to yield secondary alcohols, the script refrains from the assignment of new CIP priorities and a corresponding label. It then depends on the program used for a visualization, if an explicit wedge is used (e.g., OpenBabel), or the absence of information is highlighted (e.g., as question mark in DataWarrior, or the project of CDK depict[5]) as ambiguous. Absolute configuration of stereogenic centers (indicated in SMILES with the `@` sign) already assigned in the input however is retained.

For a selection of elements (C, N, O, P, S), the implicit description of aromatic systems (e.g., as `c1ccncc1` in pyridine, `c1c[nH]cc1` in pyrrol) is recognized. To offer a «saturation», these characters returned as upper case characters to yield e.g., piperidine (`C1CCNCC1`) and pyrrolidine (`C1C[NH]CC1`).

The script equally preserves up to one single negative, or single positive charge of these five elements (e.g., `[O-]c1ccccc1` about the phenolate anion, and `C[N+](c1ccccc1)(C)C` about *N,N,N*-trimethylbenzenaminium cation). Here, it can be sensible to «sanitize» the results this script provides by other libraries as e.g. RDKit.[6]

The capitalization of the five characters is constrained to prevent non sensible transformations of e.g., an (implicitly) aromatic atom of tin `[sn]` into the invalid form `[SN]`. Though the script is going to write tin as `[Sn]`, an adjustment of valence for elements written with two characters is beyond the current scope of the script.

A SMILES string may describe more than one molecule. Thus, the concatenation with `"."` (period character) as seen for example in descriptions of co-crystals like about 1,4-benzoquinone and hydroquinone, `C1=CC(=O)C=CC1=O.c1cc(ccc1O)O`, is retained. The example is resolved as `C1CC(O)CCC1O.C1CC(CCC1O)O`.

6 License

[5] `https://www.simolecule.com/cdkdepict/depict.html` For the mentioned annotation of CIP labels, change `No Annotation` (second pull down menu from the left) to `CIP Stereo Label`.

[6] For an overview about the freely available RDKit library, see www.rdkit.org. An introduction into the topic of «molecular sanitization» is provided in the section of this very title in the on-line RDKit Book.