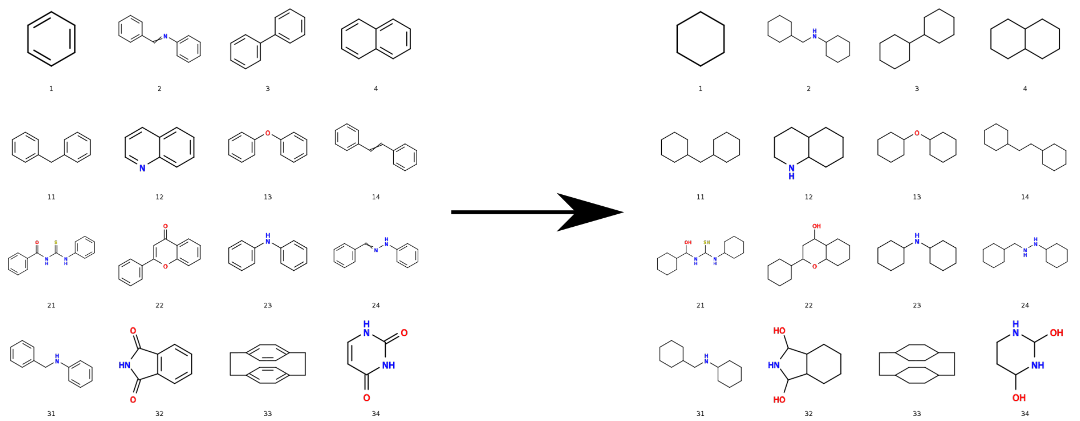
1 Background

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

The script runs from Python's CLI with a file listing SMILES to process as parameter. File `test_input.smi` (see sub-folder `test_data`) for example:

```
python saturate_murcko_scaffolds.py [test_input.smi]
```

generates `test_input_sat.smi` as permanent record; the additional `_sat` is a reminder of the performed saturation. The input file is preserved.

The use of the file extension `.smi` of the input file is a recommendation because it is one frequently seen (e.g., around OpenBabel[3]), however not mandatory. Initially written for use with either Python 2, or Python 3, the focus of the project's maintenance shifted to Python 3.

3 Example

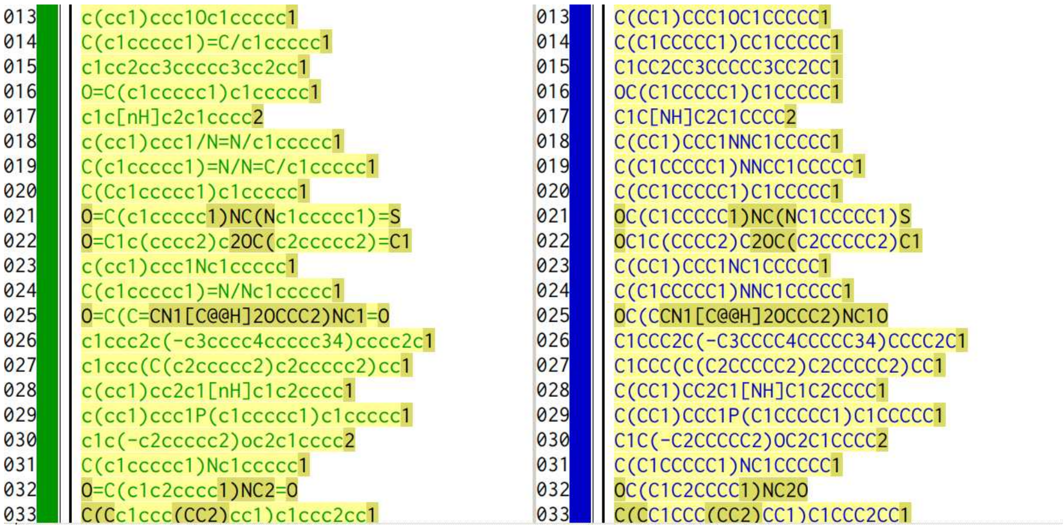
For a collection of organic materials, the Bemis-Murcko scaffolds were extracted with DataWarrior (then release 5.0.0 for Linux, January 2019) as listing `test_input.smi` including higher bond

[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) 2002–2023 by Idorsia Pharmaceuticals Ltd., is freely available under http://www.openmolecules.org. For the source code (GPLv3), see https://github.com/thsa/datawarrior.

[3] www.openbabel.org For the most recent documentation, see https://open-babel.readthedocs.io/en/latest/ReleaseNotes/ob310.html

orders (see folder `test_data`). The effect of the «artificial saturation» is easy to recognize while comparing the scaffold lists (fig. 1) in a difference view of the two `.smi` files.



```
013 c(cc1)ccc1Oc1ccccc1
014 C(c1ccccc1)=C/c1ccccc1
015 c1cc2cc3ccccc3cc2cc1
016 O=C(c1ccccc1)c1ccccc1
017 c1c[nH]c2c1cccc2
018 c(cc1)ccc1/N=N/c1ccccc1
019 C(c1ccccc1)=N/N=C/c1ccccc1
020 C(Cc1ccccc1)c1ccccc1
021 O=C(c1ccccc1)NC(Nc1ccccc1)=S
022 O=C1c(cccc2)c2OC(c2ccccc2)=C1
023 c(cc1)ccc1Nc1ccccc1
024 C(c1ccccc1)=N/Nc1ccccc1
025 O=C(C=CN1[C@@H]2OCCC2)NC1=O
026 c1ccc2c(-c3cccc4ccccc34)cccc2c1
027 c1ccc(C(c2ccccc2)c2ccccc2)cc1
028 c(cc1)cc2c1[nH]c1c2cccc1
029 c(cc1)ccc1P(c1ccccc1)c1ccccc1
030 c1c(-c2ccccc2)oc2c1cccc2
031 C(c1ccccc1)Nc1ccccc1
032 O=C(c1c2cccc1)NC2=O
033 C(Cc1ccc(CC2)cc1)c1ccc2cc1
```

```
013 C(CC1)CCC1OC1CCCCC1
014 C(C1CCCCC1)CC1CCCCC1
015 C1CC2CC3CCCCC3CC2CC1
016 OC(C1CCCCC1)C1CCCCC1
017 C1C[NH]C2C1CCCC2
018 C(CC1)CCC1NNC1CCCCC1
019 C(C1CCCCC1)NNCC1CCCCC1
020 C(CC1CCCCC1)C1CCCCC1
021 OC(C1CCCCC1)NC(NC1CCCCC1)S
022 OC1C(CCCC2)C2OC(C2CCCCC2)C1
023 C(CC1)CCC1NC1CCCCC1
024 C(C1CCCCC1)NNC1CCCCC1
025 OC(CCN1[C@@H]2OCCC2)NC1O
026 C1CCC2C(-C3CCCC4CCCCC34)CCCC2C1
027 C1CCC(C(C2CCCCC2)C2CCCCC2)CC1
028 C(CC1)CC2C1[NH]C1C2CCCC1
029 C(CC1)CCC1P(C1CCCCC1)C1CCCCC1
030 C1C(-C2CCCCC2)OC2C1CCCC2
031 C(C1CCCCC1)NC1CCCCC1
032 OC(C1C2CCCC1)NC2O
033 C(CC1CCC(CC2)CC1)C1CCC2CC1
```

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.

The work can be illustrated by OpenBabel[3] with instructions to the command line in 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.

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

4 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[4]) as ambiguous. Absolute absolute configuration of stereogenic centers (indicated in SMILES with the `@` sign) already assigned in the input file 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 positve 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 of this script by other libraries as e.g. RDKit.[5]

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.

If the input SMILES string describes more than exactly one molecule by the concatenating "`.`" (period character), then this special sign equally is written in the new SMILES string. This permits working with SMILES about e.g., co-crystals, like about 1,4-benzoquinone and hydroquinone, `C1=CC(=O)C=CC1=O.c1cc(ccc1O)O` resolved as `C1CC(O)CCC1O.C1CC(CCC1O)O`.

5 License

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[4] `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`.

[5] 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.