

Software User Manual

MOLGEN-MSF* Version 1.0.1.5

1. Introduction

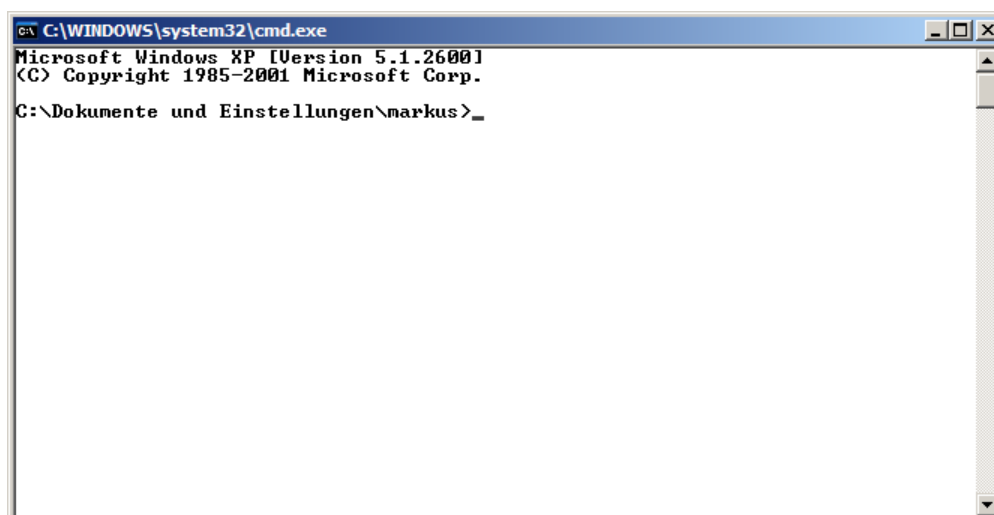
This computer program *MOLGEN-MSF* calculates match values that show how well candidate structural formulas fit low resolution (LR) electron impact (EI) mass spectra. It constructs, according to user definable fragmentation mechanisms, sets of MS fragment ions for the structure candidates and investigates how well the theoretical isotope pattern of these virtual fragment ions fit the experimental spectrum. This software can be regarded as an enhanced stand-alone version of the structure-spectra compatibility verification module of *MOLGEN-MS*¹. In contrast to *MOLGEN-MS*, which is delivered with a graphical user interface, *MOLGEN-MSF* has a command line interface that allows easy integration into batch processes for exhaustive computations. The acronym MSF is short for Match Structural Formulas.

2. Installation

To install, just copy the executable *MolgenMsf.exe* to a destination directory of your choice, e.g. `C:\Programs\MOLGEN-MS`.

3. Getting started

Command line applications are executed using the Windows *Command Prompt*. You can access *Command Prompt* via `Start | Run...` and typing `cmd.exe`. A window similar to the following will appear.



To be able to run the program, you need to change to the drive and directory where the program is installed, using the `cd` command. In the situation shown below the program was installed on drive `D:`

* Author: Markus Meringer, Munich, March 2009

and directory \Chemie\Programs\Ufz. Note that you can change the drive just by typing the drive letter followed by a colon.

```

C:\WINDOWS\system32\cmd.exe
Microsoft Windows XP [Version 5.1.2600]
(C) Copyright 1985-2001 Microsoft Corp.

C:\Dokumente und Einstellungen\markus>D:
D:\>cd Chemie\Programs\Ufz
D:\Chemie\Programs\Ufz>_
  
```

Now you can start the program by typing its name *MolgenMsf*. If your installation was successful and you have a valid license² for *MOLGEN-MS*, your screen should look like this:

```

D:\Chemie\Programs\Ufz>MolgenMsf
Error: missing argument ms
Usage: MolgenMsf ms=<filename> [msstart=<number>] [mscount=<number>]
      [mol=<filename>] [molstart=<number>] [molcount=<number>]]
      [mcp=<filename>] [mf=<filepath>] [ei] [txt]] [a] [diag] [tmv]
      [notest] [g] [log=<filename>]] [matrix] [sortms[=<number>]]
      [sortmol[=<number>]] [sortall[=<number>]]] [digits=<number>]
      [add1] [out=<filename>] [bf=<filename>] [frag=<filename>]
      [md4=<filename>]

Explanation:
ms       : mass spectra input file (msb, tra, msp)
msstart  : first mass spectrum to process
mscount  : number of mass spectra to process
mol      : molecule input file (sdf, mb4)
molstart : first molecule to process
molcount : number of molecules to process
mcp      : molcomb project file with the fragmentation reactions
mf       : location of Mass Frontier fragment input files
ei       : regard output of Mass Frontier as electron impact ions
txt      : fragment input files are text files instead of SDFfiles
a        : assign aromatic bonds
diag     : compute only diagonal elements of structure-spectra matrix
tmv      : transformation of the match value mv->1-(1-mv)^2
notest   : no test of atom states
g        : compute match value global (partial by default)
log      : output logging information and results
matrix   : write match values as matrix
sortms   : write match values as sorted lists for each molecule
sortmol  : write match values as sorted lists for each mass spectrum
sortall  : write match values as one sorted list of all ms/mol pairs
digits   : number of decimal places in the output
add1     : in the log file numbering starts at 1 (instead of 0)
out      : ms output file with explained part of the input spectra
bf       : ms output file with isotope patterns of virtual fragments
frag     : molecule output file for virtual fragments
md4      : md4 output file with matrix of molecules and match values

Description:
reads spectra and structures, calculates match values,
outputs fragments, fitted spectra, matrix of match values, etc.
  
```

Do not worry about the error message "missing argument ms". The program needs a mass spectra file as an obligatory argument.

4. Description

MOLGEN-MSF is provided as command line application and is called using the following syntax:

```
Usage: MolgenMsf ms=<filename> [msstart=<number>] [mscount=<number>]
      [mol=<filename>] [molstart=<number>] [molcount=<number>]]
      [mcp=<filename>] [mf=<filepath> [ei] [txt]] [a] [diag] [tmv]
      [notest] [g] [log[=<filename>]] [matrix] [sortms[=<number>]]
      [sortmol[=<number>]] [sortall[=<number>]]] [digits=<number>]
      [add1] [out=<filename>] [bf=<filename>] [frag=<filename>]
      [md4=<filename>]
```

Explanation:

```
ms      : mass spectra input file (msb, tra, msp)
msstart : first mass spectrum to process
mscount : number of mass spectra to process
mol     : molecule input file (sdf, mb4)
molstart: first molecule to process
molcount: number of molecules to process
mcp     : molcomb project file with the fragmentation reactions
mf      : location of Mass Frontier fragment input files
ei      : regard output of Mass Frontier as electron impact ions
txt     : fragment input files are text files instead of SDfiles
a       : assign aromatic bonds
diag    : compute only diagonal elements of structure-spectra matrix
tmv     : transformation of the match value  $mv \rightarrow 1 - (1 - mv)^2$ 
notest  : no test of atom states
g       : compute match value global (partial by default)
log     : output logging information and results
matrix  : write match values as matrix
sortms  : write match values as sorted lists for each molecule
sortmol : write match values as sorted lists for each mass spectrum
sortall : write match values as one sorted list of all ms/mol pairs
digits  : number of decimal places in the output
add1    : in the log file numbering starts at 1 (instead of 0)
out     : ms output file with explained part of the input spectra
bf      : ms output file with isotope patterns of virtual fragments
frag    : molecule output file for virtual fragments
md4     : md4 output file with matrix of molecules and match values
```

Description:

```
reads spectra and structures, calculates match values,
outputs fragments, virtual spectra, matrix of match values, etc.
```

4.1 Input

The only obligatory argument is a mass spectra file, which is specified using parameter `ms`. The program also needs structural formulas. A file with structural formulas can be input using parameter `mol`. If no such argument is given, the program tries to find structural information within the mass spectra file³.

It is possible to select certain subsets of the input spectra and structures. The parameter `msstart` is used to define the first spectrum for processing⁴. The `mscount` parameter denotes the number of spectra to be processed, starting at `msstart`. Specific molecules can be selected from the molecule file using the parameters `molstart` and `molcount`. Default values for `msstart` and `molstart` are 0 and

infinity for `mcount` and `molcount`. Thus, by default, all combinations of spectra and structures are processed.

The MS reactions can be passed to the program using parameter `mcp`. The MCP format was initially developed for *MOLGEN-COMB*⁵ and can also be used for defining ionization reactions, cleavages and rearrangement reactions in a mass spectrometer. MCP files can be opened and edited using *MOLGEN-GUI*⁶. If no MCP file is passed to the program, a set of default reactions is applied, consisting of

- n-ionization,
- n-ionization,
- σ -ionization,
- α -cleavage,
- σ -cleavage and
- 3 types of H-rearrangements,

as published recently^{7,8}.

The program can also be used to process files with fragments from external sources. Option `mf` allows importing of fragment ions produced by *Mass Frontier*⁹ instead of using the fragmentation module of *MOLGEN-MS*. More precisely, with this parameter the location of the *Mass Frontier* fragment files can be specified. *Mass Frontier* fragment files have names of the form *name_number.sdf*, e.g. *C5H13N1Isomer_1.sdf*, *C5H13N1Isomer_2.sdf*, ..., *C5H13N1Isomer_17.sdf*. The ending *_number.sdf* will be added by *MOLGEN-MSF* automatically. Although *Mass Frontier* fragment files know certain conventions for coding the ionization type in the molecular ion¹⁰, it is necessary to indicate electron impact ionization ($-e$) with the option `ei`. Otherwise protonation ($+H^+$) will be assumed as ionization type.

Finally, there is also a possibility to load molecular formulas of fragment ions from a text file. This is activated by the option `txt`. Instead of *_number.sdf* the program adds *_number.txt* to the argument specified by parameter `mf`. The content of such a text file should look as follows:

Formula	Mult
C2H6N	1
C3H8N	1
C4H10N	1
C5H11	1
C5H13N	1

The first column represents the molecular formulas of ions, the second shows their multiplicities. The multiplicities are not used for the match value calculation.

4.2 Processing

After input files are read, the program shows the number of spectra and structures found in the spectra and structure file, respectively. Depending on the size of input data, a program run may take quite a long time. While the program is running, it displays the number of the spectrum and structure being processed, to inform the user of the progress.

In molecule files, aromatic systems can either be represented by alternating single and double bonds or by a special bond type for aromatic bonds. By default *MOLGEN-MSF* processes molecules as read from input. However, using option `a` you can force *MOLGEN-MSF* to search for aromatic systems itself, and to mark the corresponding bonds. During fragmentation it is chemically more meaningful to treat aromatic bonds as such, and therefore it is strongly recommended to use this option if aromatic bonds are not already marked in the input, or if the marking is uncertain.

Using the option `diag` it is possible to calculate match values only for spectra structure pairs (1,1), (2,2) and so on. This can be useful to calculate match values only for pairs of structures and spectra belonging together.

The match value MV as implemented in the present version is defined in reference 7. This differs slightly from the match value MV' , defined in reference 8. The transformation $MV'=1-\sqrt{1-MV}$ can be enabled by option `tmv`. The first definition was also used in a recent study¹¹ comparing different tools for virtual fragmentation.

Another difference between the fragmentation in *MOLGEN-MS* and *MOLGEN-MSF* is that after each reaction step of *MOLGEN-MSF*, fragments are examined if they have valid atomic states with respect to Table 1.1 of Ref. 7 or Table 1 of Ref. 12. This feature can be disabled with option `notest`, so that the match values computed by *MOLGEN-MSF* should be equal to those of *MOLGEN-MS*.

There are a few parameters which are of minor relevance to the current release. Option `g` was used to switch to an alternative, more time consuming way of calculating the match value.

4.3 Output

The program's main outputs are match values, arranged according to mass spectra and structural formula. Using argument `log` this output can either be directed to the console (if no argument is given) or to a specified file. There are different ways to arrange these match values:

- As a matrix where rows represent structures and columns represent spectra. If this output is desired, add option `matrix`.
- As lists where each list belongs to a certain molecule, sorted by descending match values computed for the different spectra. If this output is desired add option `sortms`.
- As lists where each list belongs to a certain spectrum, sorted by descending match values computed for the different molecules. If this output is desired add option `sortmol`.
- As just one list sorted by descending match values. The structure-spectra pair with highest match value of all pairs for all spectra and structures is listed first and so on. If this kind of output is desired, add option `sortall`.

With options `sortms`, `sortmol` and `sortall`, additional values can be included to limit the lengths of the lists. Using option `digits` you can specify the number of decimal places for match values in the output

Numbering of spectra and structures starts, by default, at 0, i.e. the first spectrum/structure is represented by 0, etc. However, most humans do not think like computers and prefer to start counting at 1. If you want to have the first spectrum/structure represented by 1, please include the option `add1`.

It is possible to retrieve spectra containing explained intensities using the option `out`, followed by a filename for a spectral file (suffix `msb`, `tra` or `mss`). Using option `bf` followed by a spectral filename forces the program to output the molecular formulas of the virtual fragment ions and their calculated isotope patterns.

If you want to see the structural formulas of the fragment ions, please use option `frag` followed by a filename for a structure file (suffix `mb4` or `sdf`).

Another kind of output is an *md4* file, which — like all the other file types mentioned above — can also be opened by *MOLGEN-GUI*. This file type is originally used for coding tables, where rows represent molecular structures and columns represent molecular descriptors. However, it can also be used to show MS match values as column entries.

5. Examples

There is a file *tra-demo.tra* delivered with the program, which contains five EI mass spectra and associated structures. By typing the command

```
MolgenMsf ms=tra-demo.tra log matrix
```

the program first opens the MS file and reports the number of spectra stored inside the file:

```
spectra in file tra-demo.tra: 5
```

and then each spectra-structure pair is processed. Finally, a matrix of match values is written to the standard output:

MOL\MS	0	1	2	3	4
0	0.605	0.305	0.002	0.462	0.568
1	0.478	0.532	0.001	0.467	0.169
2	0.000	0.000	0.111	0.000	0.000
3	0.127	0.463	0.000	0.834	0.682
4	0.126	0.463	0.006	0.468	0.683

Each row represents a molecule, each column represents a spectrum. Match values range from 0 (for no match) to 1 (for full match). We see that the entries on the diagonal are always the highest in their rows and columns. This shows that among these five spectra and structures we would be able to associate structures and spectra in the correct way just by using the computer program.

Using the option *sortms* instead of *matrix* we obtain the following output:

```
MS      0      #5
MOL     0: 0.60530
MOL     1: 0.47790
MOL     3: 0.12653
MOL     4: 0.12628
MOL     2: 0.00000
```

```
MS      1      #5
MOL     1: 0.53214
MOL     3: 0.46320
MOL     4: 0.46279
MOL     0: 0.30532
MOL     2: 0.00000
```

```
MS      2      #5
MOL     2: 0.11083
MOL     4: 0.00626
MOL     0: 0.00172
MOL     1: 0.00091
MOL     3: 0.00038
```

```
MS      3      #5
MOL     3: 0.83434
MOL     4: 0.46821
MOL     1: 0.46688
MOL     0: 0.46152
MOL     2: 0.00000
```

```
MS      4      #5
MOL     4: 0.68347
MOL     3: 0.68188
```

```
MOL 0: 0.56787
MOL 1: 0.16869
MOL 2: 0.00000
```

For each spectrum the structures are sorted in order of descending match values.

Using option `sortms` we obtain sorted lists as follows:

```
MOL 0 #5
MS 0: 0.60530
MS 4: 0.56787
MS 3: 0.46152
MS 1: 0.30532
MS 2: 0.00172
```

```
MOL 1 #5
MS 1: 0.53214
MS 0: 0.47790
MS 3: 0.46688
MS 4: 0.16869
MS 2: 0.00091
```

```
MOL 2 #5
MS 2: 0.11083
MS 4: 0.00000
MS 1: 0.00000
MS 0: 0.00000
MS 3: 0.00000
```

```
MOL 3 #5
MS 3: 0.83434
MS 4: 0.68188
MS 1: 0.46320
MS 0: 0.12653
MS 2: 0.00038
```

```
MOL 4 #5
MS 4: 0.68347
MS 3: 0.46821
MS 1: 0.46279
MS 0: 0.12628
MS 2: 0.00626
```

And finally `sortall` produces the following list:

```
#pairs: 25
MS 3, MOL 3: 0.83434
MS 4, MOL 4: 0.68347
MS 4, MOL 3: 0.68188
MS 0, MOL 0: 0.60530
MS 4, MOL 0: 0.56787
```

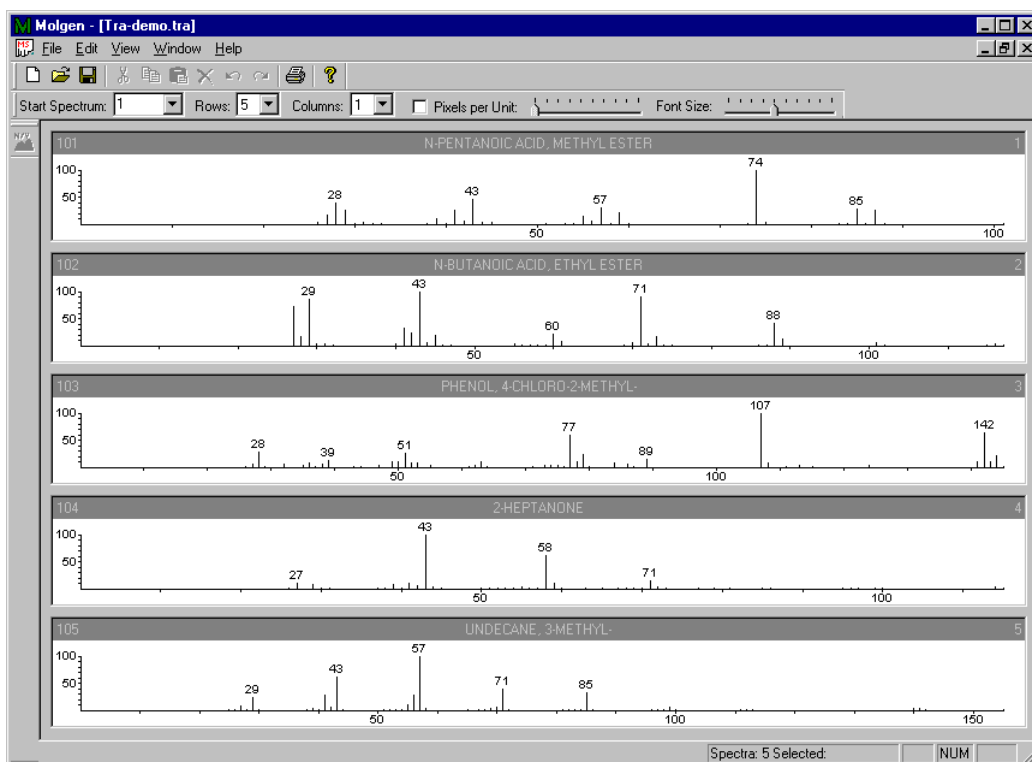
MS	1, MOL	1: 0.53214
MS	0, MOL	1: 0.47790
MS	3, MOL	4: 0.46821
MS	3, MOL	1: 0.46688
MS	1, MOL	3: 0.46320
MS	1, MOL	4: 0.46279
MS	3, MOL	0: 0.46152
MS	1, MOL	0: 0.30532
MS	4, MOL	1: 0.16869
MS	0, MOL	3: 0.12653
MS	0, MOL	4: 0.12628
MS	2, MOL	2: 0.11083
MS	2, MOL	4: 0.00626
MS	2, MOL	0: 0.00172
MS	2, MOL	1: 0.00091
MS	2, MOL	3: 0.00038
MS	4, MOL	2: 0.00000
MS	1, MOL	2: 0.00000
MS	3, MOL	2: 0.00000
MS	0, MOL	2: 0.00000

6. Advanced Features

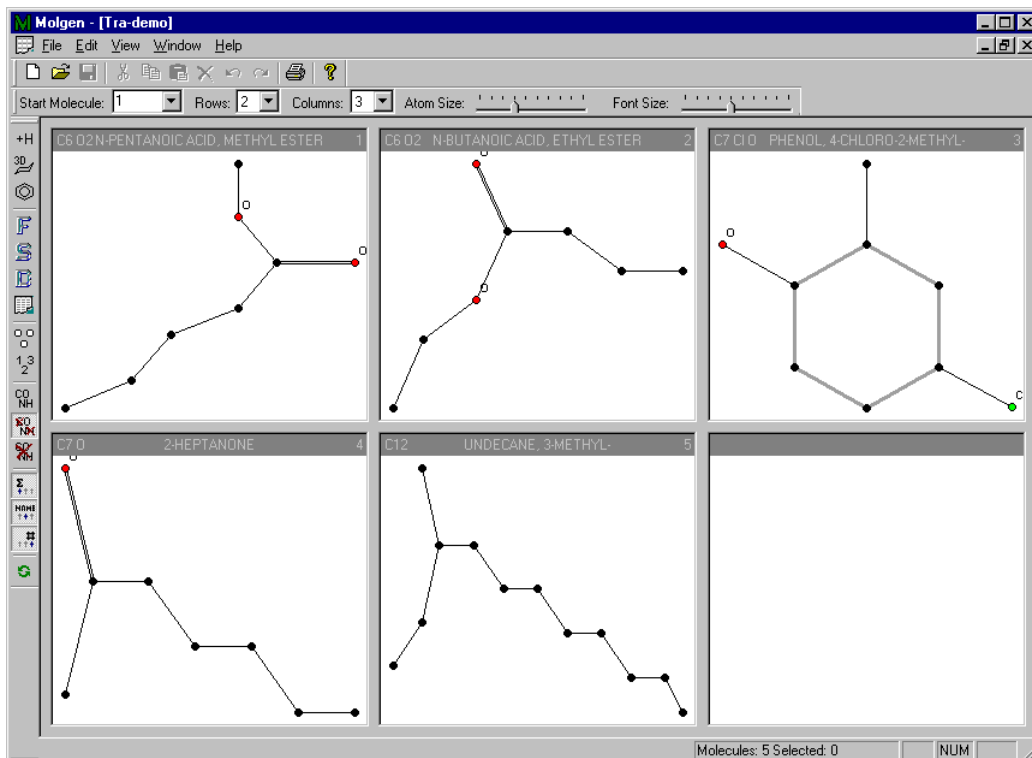
This section contains information about the visualization features of *MOLGEN-GUI*. This can help to analyze and edit input and output data of *MOLGEN-MSF*.

6.1 Viewing Spectra and Structures

Mass spectral files in *jdx* or *tra* format can be viewed in *MOLGEN-GUI* by selecting *File/Import...* or just by dragging the spectral file from Windows Explorer and dropping it on the *MOLGEN-GUI*'s main window.



For certain file formats, structures can be stored within the spectra file. These structures can be viewed via *File/Molecules*.



In the figure above there are no H atoms stored with the structures. Hydrogen atoms can be added to the structures by calling *File/Hydrogen...* and can be displayed by enabling *View/Hydrogens*.

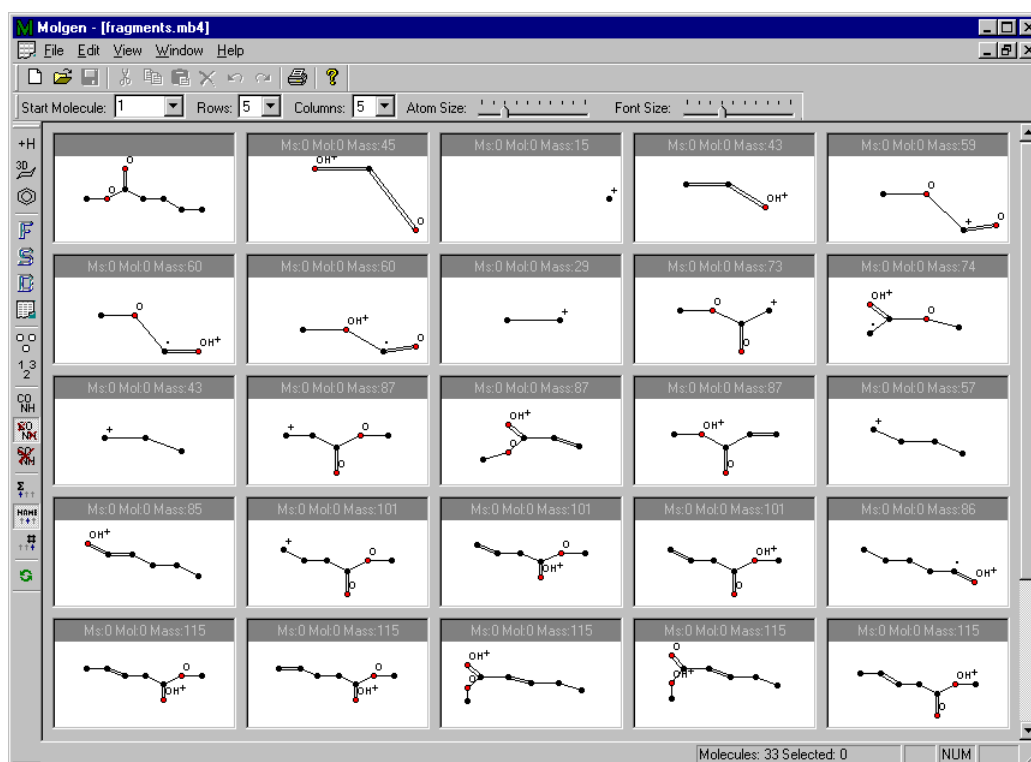
MOLGEN-GUI also offers interfaces to other spectral file formats. In order to import mass spectra given as *ASCII peak list (*.txt)*, *NIST mass spectra file (*.msp)* or *ChemStation ASCII file (*.csv)* format, proceed as follows: create a new mass spectra document by *File/New/More...* and select *Mass Spectra* from the list. Using *File/Append...* you can now add single spectra in the above mentioned formats. Of course, you can save the newly created mass spectra document in MOLGEN-GUI's internal (binary) mass spectra format *msb* with *File/Save as...*, or as *JCAMP-DX* or *TRANSPEC* file using *File/Export...*

6.2 Viewing Fragments

As already mentioned in Section 4.3, MOLGEN-MSF is able to write the fragment ions generated to the output. Using the command:

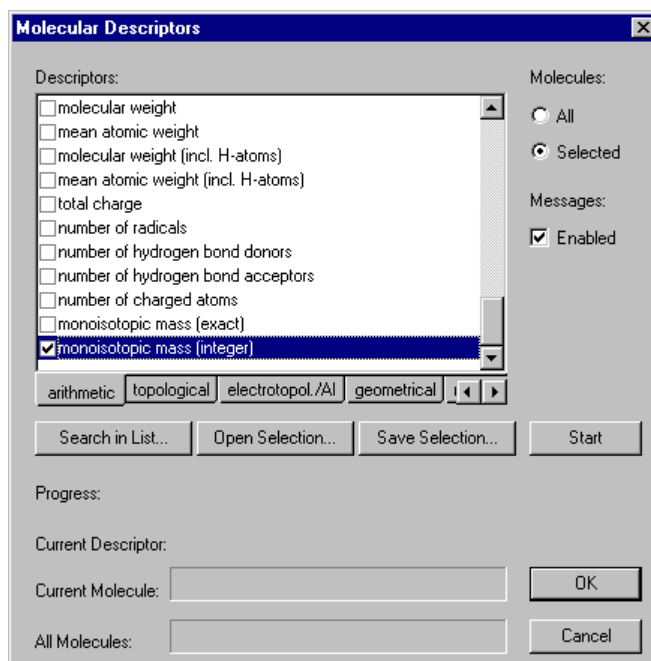
```
MolgenMsf ms=tra-demo.tra mscount=1 molcount=1 frag=fragments.mb4
```

the first spectrum and structure from file *tra-demo.tra* are processed and the fragment ions generated are stored in the file *fragments.mb4*.¹³ You can open this file in MOLGEN-GUI with *File/Open...* or just by *Drag & Drop*. A part of the structures are depicted below. The first structure in the file is the molecule under consideration itself, followed by a set of fragment ions. In this specific example, 32 fragment ions were generated. Each structure is supplied with a header, which contains text such as *Ms: 0 Mol:0 Mass:...* This header is important in case you process more than one spectra-structure pair in a program run. Using this header you are able to identify which computation generated that specific fragment.

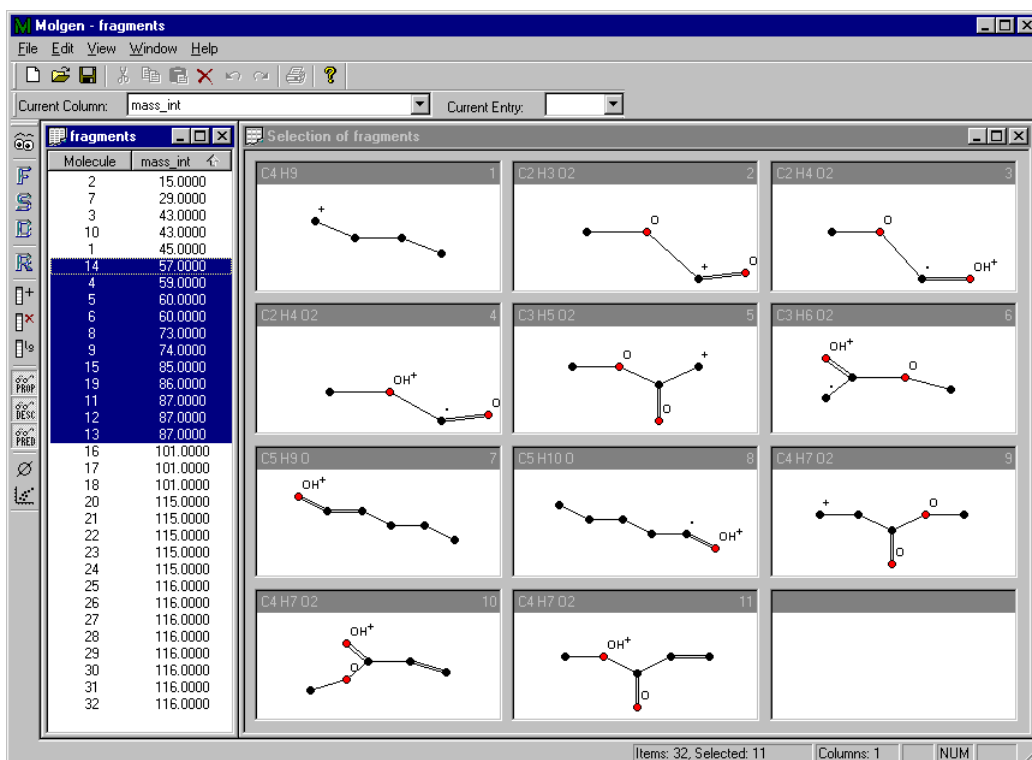


You might have noticed that the fragments are not sorted strictly according to ascending mass. Indeed they are just written to the output in the order they were generated. However, there is a workaround within MOLGEN-GUI that allows you to sort the fragments with by ascending (or descending) mass. For this purpose we use MOLGEN-GUI's abilities to calculate molecular descriptors

in the following way: select all fragment ions using left mouse click, SHIFT and/or SHIFT+CTRL. Selected structures will be highlighted with a blue header. Now call *File/Indices...* and check the *monoisotopic mass* descriptor as demonstrated below. By clicking the *Start* button, monoisotopic masses will be calculated, and upon clicking *OK* the *Molecular Descriptors* dialogue will close and a table with two columns named *Molecule* and *mass_int* will appear.



Clicking on the column header of the *mass_int* column sorts the table according to increasing or decreasing mass. By selecting some or all rows of the table and calling *File/Molecules*, a new structure window appears with fragment ions sorted according to their masses.

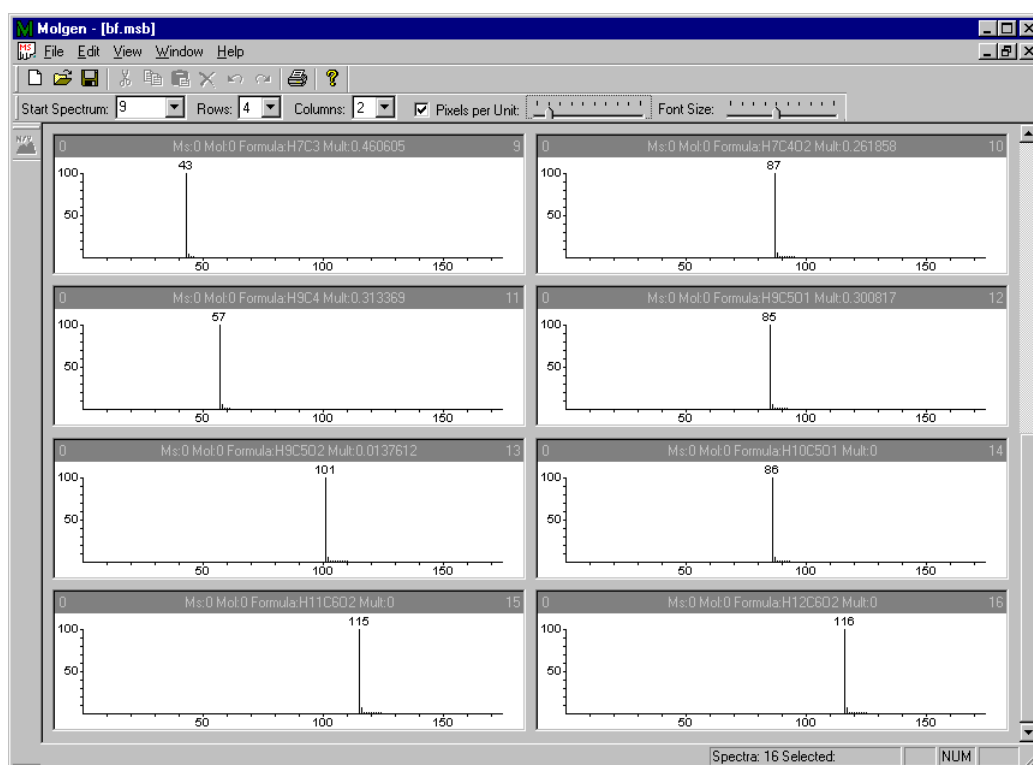


6.3 Viewing Fragment Formulas and Calculated Isotope Patterns

Another feature of *MOLGEN-MSF* is its ability to write the molecular formulas of fragment ions and their calculated isotope distributions to the output. The data for the example depicted below was calculated with the command

```
MolgenMsf ms=tra-demo.tra mscount=1 molcount=1 bf=bf.msb
```

The file *bf.msb* can be opened with *MOLGEN-GUI*. This contains several spectra, each with a single peak group only. Each spectrum has a header, which contains information about structure and spectrum of the computation (trivially 0 in this example), followed by the molecular formula of the fragment ion and finally a factor between 0 and 1 which shows how this certain isotope pattern contributed to fitting the experimental spectrum.



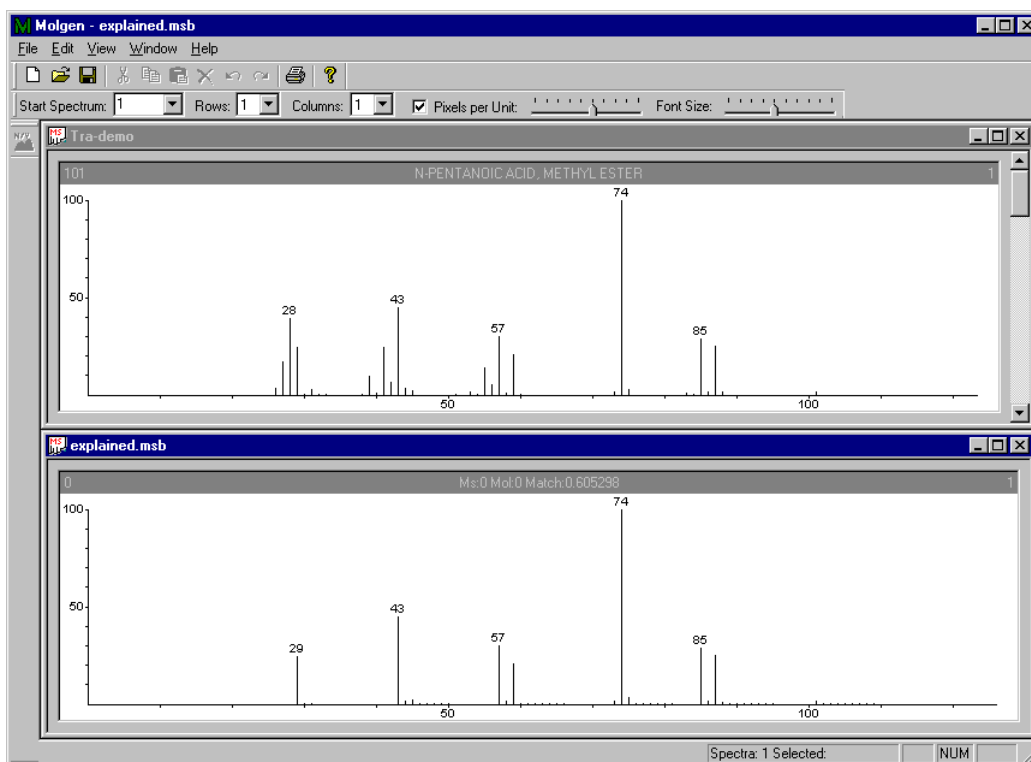
In this certain example, fragment ions belonging to 16 different molecular formulas were generated. This can easily be read in *MOLGEN-GUI*'s status bar, in the lower right corner.

6.4 Viewing Explained Parts of Experimental Spectra

As already mentioned earlier, *MOLGEN-MSF* is also able to write the explained part of the experimental spectrum to the output. In order to demonstrate this feature we execute

```
MolgenMsf ms=tra-demo.tra mscount=1 molcount=1 out=explained.msb
```

The file *explained.msb* can be opened with *MOLGEN-GUI* and be compared to the experimental spectrum as depicted below.

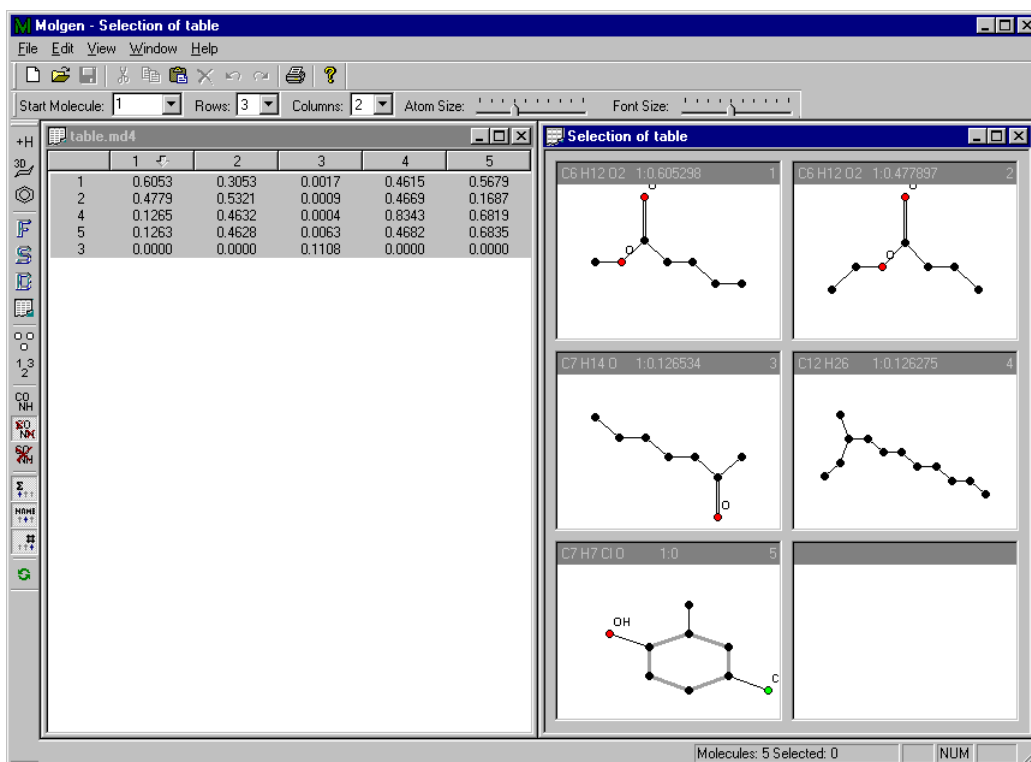


6.5 Viewing Matchvalues as Table inside MOLGEN-GUI

By using option *md4* it is possible to create a table with linked structures that can be opened with *MOLGEN-GUI*. The command

```
MolgenMsf ms=tra-demo.tra md4=table.md4
```

produces a file named *table.md4*. When you open it with *MOLGEN-GUI* a table appears, where every row represents a structure and entries in the columns show match values for the structure-spectra pairs. As already mentioned in Section 6.2, the rows can be sorted according to a column of your choice by clicking the appropriate column header. If you check *File/Pass Values*, select all rows and then call *File/Molecules*, you get a window with all structures sorted by descending match values. The values themselves can be read in the structure headers. This feature might be useful, for example, if you want to catch a quick view of your top ranked candidates.



6.6 Viewing and Manipulating Fragmentation Reactions

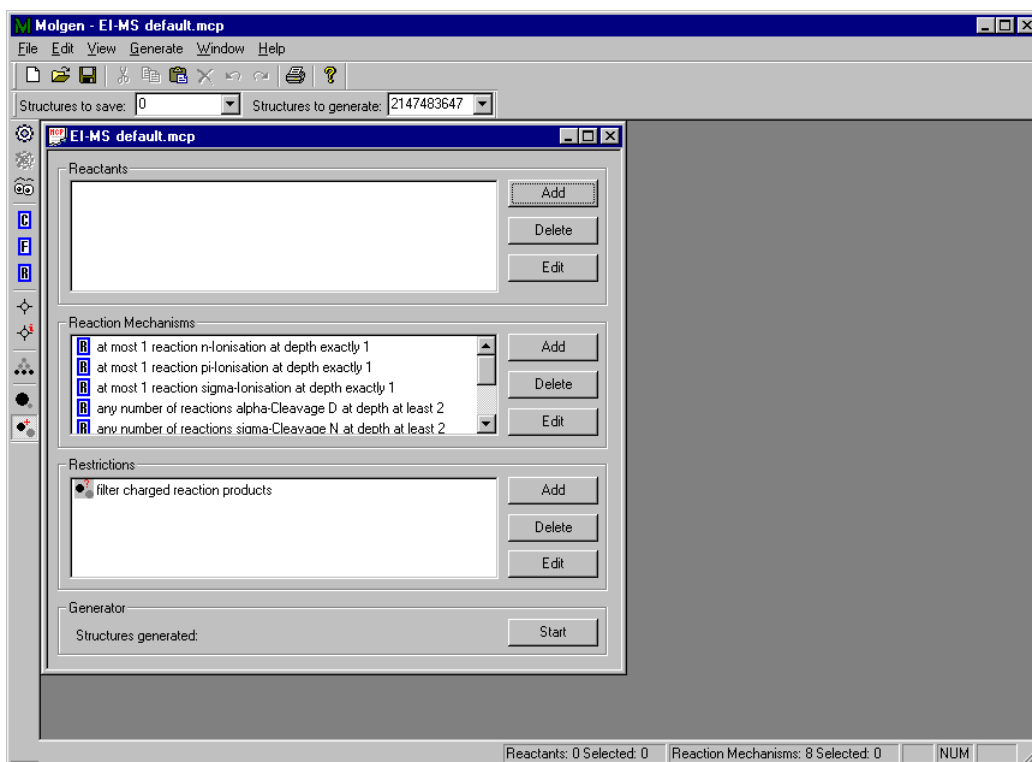
By default there are a total of 8 reactions used by *MOLGEN-MSF*, three ionization reactions:

- n-ionization,
- π -ionization,
- σ -ionization,

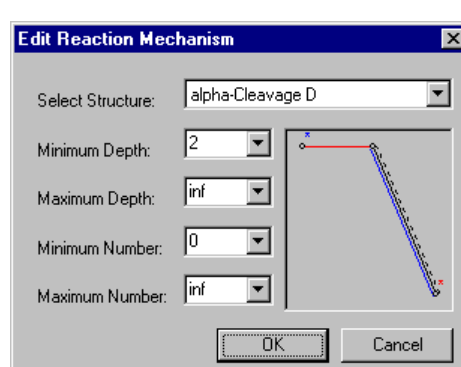
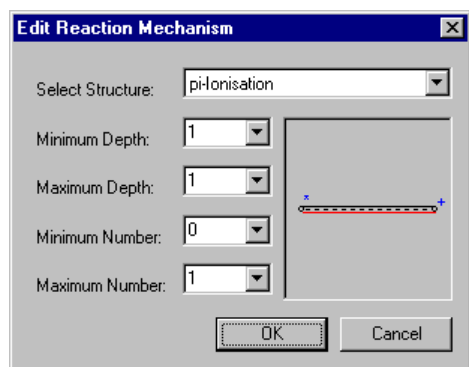
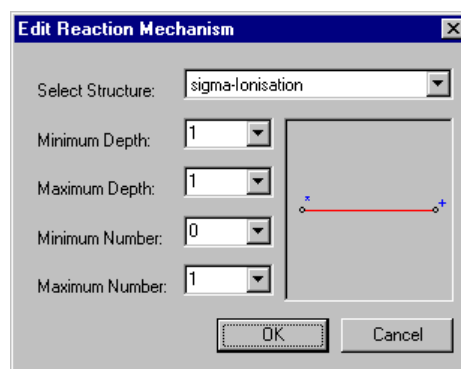
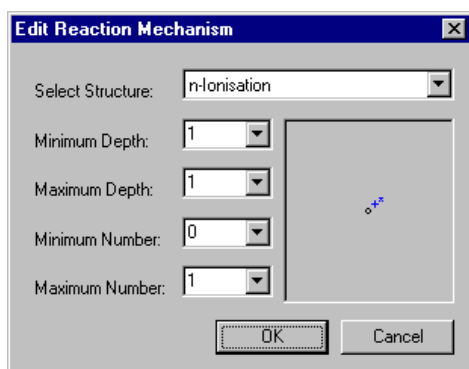
two types of cleavages:

- α -cleavage,
- σ -cleavage,

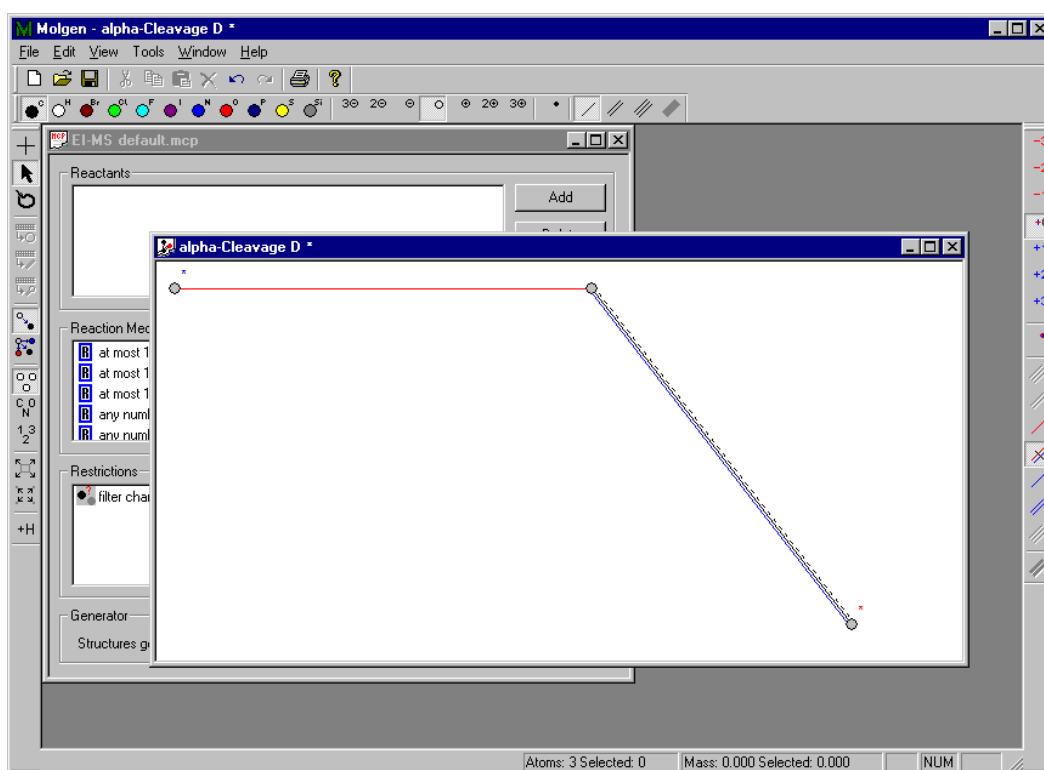
and three types of H-rearrangements (on 4, 5 and 6 atoms). The set of reactions can be viewed and changed using *MOLGEN-GUI*. The figure below shows the user interface with the default file of EI-MS fragmentation reactions.



The reactions are grouped in the *field Reaction Mechanisms*. Each of them can be edited by selecting the appropriate row and by clicking the *Edit* button (or just a double click on the appropriate row). Then windows similar to the following appear.



In the dialogue window you see the name of the reaction in the uppermost edit box. On the left side there are edit boxes labeled *Minimum Depth*, *Maximum Depth*, *Minimum Number* and *Maximum Number*. These entries define the application of reactions during a reaction based structure generation. For the generation of MS fragments it is only important to have two different settings, one for ionizations (1, 1, 0, 1) and one for proceeding reactions (2, inf, 2, inf), i.e. cleavages or rearrangements. Furthermore, we see on the right side a sketch of the reaction mechanism. Red lines denote bonds that are broken during the reaction, blue lines denote bonds that are built during a reaction. Stroke lines represent alternatives for bonds. For each atom, charges and changes in charges can be specified, as well as unpaired electrons and changes in unpaired electrons. Details on the definition of reactions and reaction-based structure generation are published in a recent article.¹⁴ By right mouse clicking on the reaction mechanism, a context menu appears. When you choose *Moled*, a copy the reaction mechanism appears in a larger window and it can be edited here.



Notes and References

- ¹ A. Kerber, R. Laue, M. Meringer, K. Varmuza. MOLGEN-MS: Evaluation of Low Resolution Electron Impact Mass Spectra with MS Classification and Exhaustive Structure Generation. Volume 15 of *Advances in Mass Spectrometry*, pages 939-940. Wiley, 2001.
- ² For contact information see www.molgen.de.
- ³ For certain spectra file formats (e.g. tra, msb) it is possible to store structural information within the spectra file.
- ⁴ Counting starts at 0.
- ⁵ R. Gugisch, A. Kerber, R. Laue, M. Meringer, J. Weidinger: MOLGEN-COMB, a Software Package for Combinatorial Chemistry. *MATCH Communications in Mathematical and in Computer Chemistry* 41, 189-203, 2000.

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- ⁶ There is still no 'official name' for the GUI, so for the time being it is simply called MOLGEN-GUI.
- ⁷ M. Meringer: *Mathematical Models for Combinatorial Chemistry and Molecular Structure Elucidation*. Logos Verlag Berlin, 2004. In German.
- ⁸ A. Kerber, M. Meringer, C. Rücker: CASE via MS: Ranking Structure Candidates by Mass Spectra. *Croatica Chemica Acta* 79, 449-464, 2006.
- ⁹ Mass Frontier 5.0, HighChem Ltd., Bratislava, Slovakia.
- ¹⁰ For the molecular ion there is an additional C atom coded in the atom block. In the properties block this atom is assigned an alias "+" for EI ionization, "+H+" for protonation and "-H+" for deprotonation.
- ¹¹ E.L. Schymanski, M. Meringer, W. Brack: Matching Structures to Mass Spectra using Fragmentation Patterns – Are the results as good as they look? To appear in *Analytical Chemistry*, 2009.
- ¹² A. Kerber, R. Laue, M. Meringer, C. Rücker: Molecules in Silico: The Generation of Structural Formulae and Applications. *Journal of Computer Chemistry, Japan* 3, 85-96, 2004.
- ¹³ *mb4* is *MOLGEN-GUI*'s internal file format for storing molecular structures. As binary format it is more space- and time efficient than ASCII exchange formats as e.g. *sdf*.
- ¹⁴ A. Kerber, R. Laue, M. Meringer, C. Rücker: A Graph Description of Chemical Reactions. *Journal of Chemical Information and Modeling* 47, 805-817, 2007.