4,4-Diethyl-17-hydroxy-17α-methyl-3-oxoandrost-5-ene-2α-carbonitrile (**6a**) – from **5a**. Yield 69%; m.p. 135–140° (C_6H_6); $[\alpha]_D^{25} = -33.8°$; UV. max 240 (ε 7930).

$C_{25}H_{37}NO_2$ (383.6) Calc. C 78.28 H 9.72 N 3.65% Found C 78.47 H 9.83 N 3.81%

1,4'-Spiro[cyclopentane-17'-hydroxy-17'α-methyl-3'-oxoandrost-5'-ene-2'α-carbonitrile] (**6c**) – from **5c**. Yield 65%; m.p. 150–152° (EtOAc); $[\alpha]_D^{25} = -20.0°$; UV. max 239 (ε 5810).

$C_{25}H_{35}NO_2$ (381.5) Calc. C 78.68 H 9.25 N 3.67% Found C 78.42 H 8.99 N 3.59%

4,4-Diethyl-17α-methylandrost-5-eno[3,2-c]pyrazol-17-ol (**9a**) – from **4a**. Yield 80%; m.p. 229–233° (EtOH); $[\alpha]_D^{25} = -50.9°$; UV. max 224 (ε 5690).

$C_{25}H_{38}N_2O$ (382.6) Calc. C 78.48 H 10.01 N 7.32% Found C 78.42 H 9.76 N 7.31%

1,4'-Spiro[cyclohexane-17'α-methylandrost-5'-eno(3',2'-c)-pyrazol-17'-ol] (**9b**) – from **4b**. Yield 93%; m.p. 278–280° (EtOAc); $[\alpha]_D^{25} = -62.8°$; UV. max 223 (ε 5340).

$C_{26}H_{38}N_2O$ (394.6) Calc. C 79.14 H 9.17 H 7.10% Found C 79.20 H 9.12 N 7.33%

1,4'-Spiro[cyclopentane-17'α-methylandrost-5'-eno-(3',2'-c)-pyrazol-17'-ol] (**9c**) – from **4c**. Yield 88%; m.p. 266–270° (EtOH); $[\alpha]_D^{25} = -67.9°$; UV. max 224 (ε 5820).

$C_{25}H_{36}N_2O$ (380.6) Calc. C 78.90 H 9.54 N 7.36 Found C 78.64 H 9.36 N 7.07%

REFERENCES

[1] *Helmut C. Neumann*, J. med. Chem. *14*, 1246 (1971).

[2] *A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler & R. O. Clinton*, J. med. Chem. *6*, 1 (1963).

[3] a) *G. O. Potts, D. F. Burnham & A. L. Beyler*, Federation Proceedings *22*, 166 (1963).
b) *D. F. Burnham, A. L. Beyler & G. O. Potts*, Federation Proceedings *22*, 270 (1963).

[4] *A. L. Beyler, G. O. Potts & D. F. Burnham*, First International Congress of Endocrinology, 1960, Abstracts, pp. 829–830.

[5] *B. R. Brown, P. W. Trown & J. M. Woodhouse*, J. chem. Soc. *1961*, 2478.

[6] *M. S. Newman, V. De Vries & R. Darlak*, J. org. Chemistry *31*, 2171 (1966).

[7] *R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson & Clarissa Carabateas*, J. Amer. chem. Soc. *83*, 1478 (1961).

194. Heuristic Programming as an Ion Generator in Mass Spectrometry

I. Generation of Primary Ions with Charge Localization

by **Allan B. Delfino** and **Armand Buchs**

Department of Physical Chemistry,
University of Geneva, 1211 Geneva 4, Switzerland.

(3 V 72)

Résumé. Un programme connu sous le nom de *ION GENERATOR* a été élaboré. Pour le moment ce programme est capable de créer, à partir de n'importe quelle molécule organique, les ions primaires résultant de la fragmentation de l'ion moléculaire et de proposer des mécanismes de fragmentation pour expliquer la formation des ions.

In this paper we present a heuristic program we have devised to simulate the formation of ions in the ion source of a mass spectrometer. Our program, the *ION GENERATOR*, acts in much the same way as the chemist who is trying to rationalize ion formations with the help of paper and pencil; it is based on the well known method

of electron book-keeping. The program is expandable to include in the future a great proportion of the mechanistic steps delineated for example in the textbook by *Djerassi et al.* [1]. With such a program one can expect to generate, from any molecule, a number of important ions present in a mass spectrum. The advantages of using a computer to look for fragmentation mechanisms are manyfold, but we would like to name two which we consider to be of primary importance. Since the electron book-keeping method is tedious, the chemist usually stops when he has realized a plausible rationalization of the fragmentation. But the computer will realize an *exhaustive* and *irredundant* set of plausible rationalizations that are consonant with the structures of the formed ions and that are not chemically unsound. Hence, the chemist who utilises the program could then design, on the basis of the proposed fragmentation paths, labelling experiments to determine which of the sets present indeed the best rationalizations, or which fragmentation modes are occuring simultaneously.

The second reason for interest in this kind of research is the fact that the methods of electron book-keeping were handed down by examples, after presenting of a few rules. If one wants a computer to handle electron book-keeping, a much more rigorous presentation must be worked out. One is compelled to generalize, as much as can be done, each and every step of a fragmentation process. Besides the research described here, another area of research where heuristic search techniques are applied to mass spectrometry has recently been published by *Buchanan et al.* [2].

In order to generate molecular ions from a molecule and to fragment them to form all plausible primary ions, the *ION GENERATOR* program must know the motivations and methods of altering structures, which we call primitive operations. By applying these primitive operations in all plausible sequences to a molecule, or to an ion, until the program finds a new ionic species different in mass from the parent species, it builds sets of primitive operations which represent fragmentation mechanisms and which yield ions of various masses.

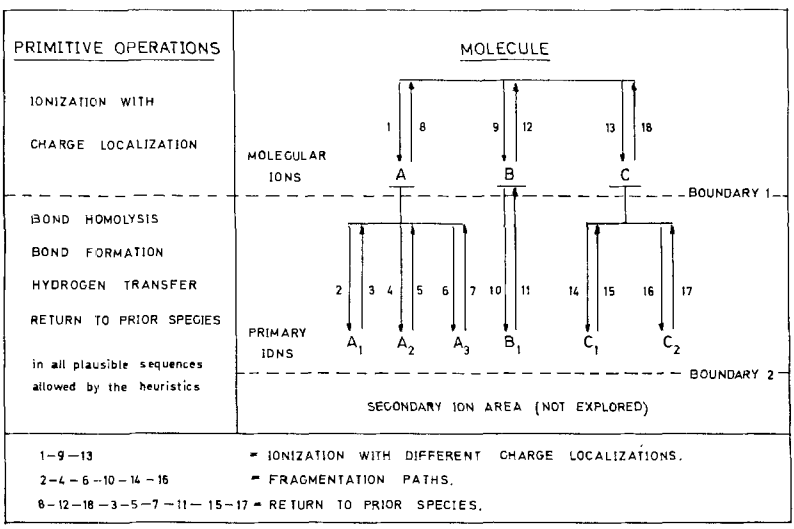


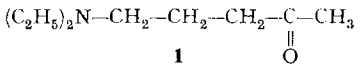
Figure 1. *Sequence of operations to ionize and fragment molecules.*

The primitive operations the program currently contains are the following:

- Ionization with charge localization,
- Bond homolysis β to a radical site,
- Bond formation between two adjacent radical sites,
- Transfer of a hydrogen atom to a radical site *via* cyclic transition states of various sizes.

The moves the program performs to get from a molecule to the primary ions, i.e. only to those ions which have the molecular ions as direct precursors, are illustrated in Fig. 1. As is shown in this Figure, for the time being, the program stops its work at boundary 2, after it has formed all plausible primary ions[1]). A particular mechanism will then be substantiated if the program finds in the actual mass spectrum a signal due to the ion generated through the mechanism.

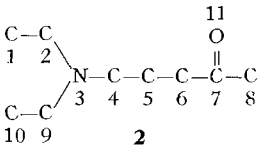
The way the program applies the primitive operations will be illustrated with an example, the ionization and fragmentation of 5-diethylamino-pentan-2-one (**1**).



1

Input of the data to the program. – The data submitted to the *ION GENERATOR* are a structure and its low resolution mass spectrum. The mass spectrum is given to the program as pairs of mass-intensity integer values. The first card is a title card which serves to identify the compound. The mass-intensity cards which follow the title card are punched with pairs of integers; four columns are reserved for the mass, followed by four columns for the corresponding intensity.

The input of the structure is explained by using the example 5-diethylamino-pentan-2-one (**1**). The atoms are first numbered in an *arbitrary* way. To make the input coding as short as possible, the longest chain of singly bonded atoms should be searched for and the atoms of that chain should be numbered in sequence. A convenient way to number the atoms of structure **1** is shown below (**2**).



2

All the atoms found in the longest chain, i.e. atom No. 1 through atom No. 8 are considered as a group of atoms. The first structure input card, which follows the last spectrum input card, is the *ATOM CARD*, which specifies what kind of atom each number represents. The chemical symbols of the atoms are punched in the columns corresponding to the assigned numbers. For structure **1** numbered as shown in **2**, the *ATOM CARD* would be as follows (**3**).

Column	1	2	3	4	5	6	7	8	9	10	11
Symbol	C	C	N	C	C	C	C	C	C	C	O

3

The program accepts up to fifty atoms not counting the hydrogen atoms.

BOND CARDS follow the *ATOM CARD*. They describe how the atoms are connected in the structure. There are no restrictions about representing structures with rings. The program is equipped to handle any structure which can be found in organic chemistry. The first column

[1]) The program can generate any depth in the ionic area, but lack of heuristics beyond boundary 2 (Fig. 1) prevents excursion in the ionic area retaining plausibility.

of a *BOND CARD* is used to differentiate between connections through a group of atoms and connections between two atoms only; the digit '1' is punched in that column for a group and the digit '0' for connections between two atoms only. The next two sets of three columns are used for the numbers assigned to the first and to the last atom of the chain. The eight and last column transmits the information about the bond order, i.e. 1, 2 or 3 for single, double and triple bonds, respectively.

With the numbering shown in **2** the *BOND CARDS* to input the structure of 5-diethylamino-pentan-2-one are the following (**4**):

BOND CARD No	*Columns*							
	1	2	3	4	5	6	7	8
1	1			1			8	1
2	0			9			3	1
3	0			9		1	0	1
4	0			7		1	1	2

4

These four *BOND CARDS* transmit the following information:

CARD No. 1: From atom No. 1 to atom No. 8 there is a group of atoms where each atom is connected to the following one in number by a single bond.

CARD No. 2: Atom No. 9 is connected to atom No. 3 by a single bond.

CARD No. 3: Atom No. 9 is connected to atom No. 10 by a single bond.

CARD No. 4: Atom No. 7 is connected to atom No. 11 by a double bond.

These cards can be given to the program in any sequence. The number of *BOND CARDS* needed to input a structure depends on how the atoms are numbered. The number of cards can always be minimized by choosing the appropriate numbering sequence.

Notational scheme for the output of chemical structures. – To present the structures of the ions and of the neutral species formed as a result of applying the primitive operations to a molecule or to an ion, a notation similar to *Lederberg*'s *DENDRAL* notation is used [3]. The differences between the linear notation used here and the *DENDRAL* notation are that our notation shows the hydrogen atoms of the structure and also indicates on which atoms radical sites and positive charges are found. Moreover, the notation used here has no canonical order. The *DENDRAL* notation has recently been nicely explained by *Buchanan et al.* in a review paper [4].

The two general rules of the notation used by the *ION GENERATOR* are:

Rule 1: An atom is printed along with its hydrogen atoms, followed by its free bonds.

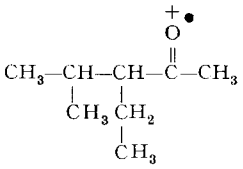
Rule 2: The radical(s) attached to the free bond(s) of an atom are printed in the same order as were the bond(s) according to rule 1.

The following examples illustrate both rules.

1. CH2——CH3OH $\quad$ $CH_3—CH_2—OH$

2. NH2—CH——CH2—CH2—OHCH3 $\quad$ $H_2N—\underset{\displaystyle CH_3}{\underset{|}{CH}}—CH_2—CH_2—OH$

As an example of a ionic species one can consider the following structure (**5**):



5

The linear notation for this structure can be written as (**6**).

CH3—CH——CH3CH——CH2—CH3C=—O(+.)CH3

6

Ionization and charge localization. – In mass spectrometry, rationalization of bond cleavages by the electron book-keeping method assumes that in a molecular ion the charge is preferentially located at favorable sites, just prior to fragmentation. It is not unreasonable to think about the primary ions as originating from different molecular ions. These molecular ions could differ with respect to the charge locus, to their relative stability, linked to their tendency to fragment before they can rearrange. Functional groups containing heteroatoms generally provide the best loci for the positive charge. Carbon-carbon multiple bonds also play an important role while carbon-carbon single bonds and carbon-hydrogen bonds are much less effective. The program has been designed to know that the most likely occurring molecular ions are those where the active site arises by removal of a non-bonding electron, followed by those in which the expelled electron is a Π type electron. It also knows which heteroatoms are more effective than others to stabilize the positive charge. For each kind of electron type and for each environment a unique ionization threshold value has been semi-empirically chosen. Table 1 shows threshold values for a number of struc-

Table 1. *Threshold values for ionization.*

Substructure	—N<	—NH	—NH_2	>C=S	>C=O	—S—	—O—	—SH
Ionization threshold value	1000	950	900	850	800	750	700	650

Substructure	—OH	—C=C—	>C=C<		—CH—	—CH_2—	
Ionization threshold value	600	550	500	450	400	350	300

tural environments. These values, which range arbitrarily from 300 to 1000, allow the user of the program to select, by means of an option card, the kind(s) of ionization that he wants the structure to undergo. For example, if one wants ionization to take place only on the heteroatoms present in a molecule, one will select a range extending from 600 to 1000. In a difunctional molecule, it is possible to generate the ions arising from charge localization on the two heteroatoms separately. The program would have to be run twice, each time with the appropriate range for the ionization threshold values. For any chosen range, including the whole range, i.e. 300 to 1000, the *ION GENERATOR* builds the molecular ions and fragments them in order of decreasing threshold values.

Bond homolysis and bond formation. – The only motivation currently known to the program to homolyze a particular bond is the availability of a radical site in a β position. This allows, afterwards, the formation of a new bond either in the ionic or in the neutral species. Another requirement a particular bond must satisfy in order to be fissionable is that it must not have been formed by the *ION GENERATOR*

in a previous operation of the ongoing fragmentation mode. Regarding C–H bond cleavages, the program considers all such bonds as equivalent when they originate from the same atom. Only one of the equivalent bonds will be homolyzed. Each time an ion has been formed, the program searches the mass spectrum for the relative abundance of the peak corresponding to the ion and prints it out, along with the structures of the ionic and neutral (if any) species. Even homolytic cleavages which do not change the mass of an ionic species are performed by the program. This affords a way to create a new radical site which can then play the trigger role for the next step of the fragmentation mode. However, homolysis performed on a double bond is not allowed to be the last step of a sequence of primitive operations; a fragmentation mechanism always ends with an ionic species having a mass which is smaller than the mass of the precursor ion.

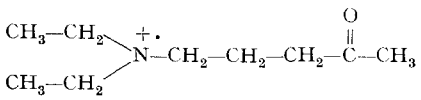
Transfer of a hydrogen atom to a radical site via *cyclic transition states of various sizes.* – The tendency of a radical site to form a new bond can also be satisfied by the transfer of a hydrogen atom to the radical site. This creates a new radical site which is then able either to induce β-cleavage or to trigger a new hydrogen transfer. The sizes of the cyclic transition states which are presently allowed are from four- to eight-membered rings. Some loose restrictions are placed on the sizes which are allowed. Thus, for example, a hydrogen atom cannot be abstracted from a carbon atom bearing a double bond, or from an atom on which a hydrogen atom has already been transferred during a previous operation of the ongoing mechanism. Situations leading to blatant strain are also avoided. Moreover, the *ION GENERATOR* allows only two transition states to occur in any sequence of primitive operations. This restriction is based on the fact that extensive rearrangement before fragmentation, leading to drastic scrambling of the hydrogen atoms, is contrary to the ability of mass spectrometry to elucidate structures.

Mechanisms proposed by the ION GENERATOR for the formation of primary ions from 5-diethylaminopentan-2-one (**1**). – The ionization range which was selected extended from 750 to 1000. From Table 1 it can be seen that ionization then occurs only on the two heteroatoms. Two molecular ions were thus generated, one by lone-pair ionization on the nitrogen atom (atom No. 3 according to the numbering shown in **2**) and the other by lone-pair ionization on the oxygen atom (atom No. 11).

The program returns two kinds of outputs. On the main output every step of the various processes leading to the formation of an ion is shown in detail, with the structures of both the ionic and neutral (if any) species printed in the linear notation. A second output shows what occurred in a shorthand notation. The structures of the two molecular ions as they are printed are shown below with their respective translations (**7** and **8**).

Molecular ion No. 1

CH3–CH2–N(+.)–CH2–CH2–CH2–C(=O)–CH3OCH2–CH3 i.e.



7

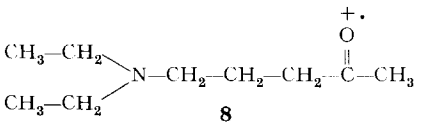
The abbreviated notation for that process is printed as follows:

ION 3 IMASS 157 INT 5,1% NMASS 0, which means:

'ionization affects atom No. 3, mass of the ionic species is 157, relative abundance of the peak found in the actual mass spectrum is 5,1%, mass of the neutral fragment lost is zero'.

Molecular ion No. 2

N———CH2—CH3CH2—CH2—CH2—C=—O(+.)CH3CH2—CH3 i.e.



8

The abbreviated notation is:

ION 11 IMASS 157 INT 5,1% NMASS 0

From these two molecular ions the program generated altogether 16 ions of different masses by various mechanisms. The list of the ions which were generated is

Table 2. *Number of mechanisms proposed for the formation of primary ions from 5-diethylamino-pentan-2-one.*

Ionization on nitrogen					Ionization on oxygen				
	Mechanisms involving			Total number of mechanisms	Mechanisms involving			Total number of mechanisms	Intensity[a]) %
	0 H transfers	1	2		0 H transfers	1	2		
m/e									
43					1	0	2	3	52,8
44					0	0	1	1	5,1
58					0	1	1	2	26,4
71					0	0	2	2	3,6
72	0	0	3	3					3,4
73	0	1	1	2					1,0
85					0	0	1	1	30,5
86	1	0	0	1	0	1	2	3	100,0
87	0	1	1	2					11,0
100	0	0	3	3					0,8
114	0	1	1	2					0,6
115	0	1	0	1					0,1
128	0	0	3	3	0	0	1	1	0,2
129	0	1	0	1					0,1
142	1	0	0	1	1	0	0	1	3,6
156	2	0	0	2					0,8
157				1				1	5,1
				22				15	

[a]) Intensity values refer to relative abundances with intensity of the base peak = 100%.

shown in Table 2 along with the number of non-equivalent mechanisms proposed for the formation of each ion. In the structure of **1**, carbon atoms No. 1 and No. 2 are respectively equivalent to carbon atoms No. 10 and No. 9. Equivalent mechanisms involving these carbon atoms have been counted once only. Moreover, when transfer of hydrogen atoms occurs, only those mechanisms which could be, if desired, subjected to direct experimental proof by means of labelling with deuterium, have been retained in Table 2. Mechanisms in which all the rearrangements of hydrogen atoms are internal to the product ion, or to the expelled neutral fragment, have been rejected manually.

Table 3. *Mechanisms proposed for the fragmentation of 5-diethylamino-pentan-2-one down to primary ions*

m/e	Mechanisms proposed					Order
43	ION 11	HOM 6,7	MKB 7,11			25
	ION 11	6MRTH4	6MRTH8	HOM 6,7	MKB 7,11	29
	ION 11	8MRTH9	8MRTH8	HOM 6,7	MKB 7,8	37
44	ION 11	8MRTH9	5MRTH5	HOM 6,7		34
58	ION 11	6MRTH4	HOM 5,6			26
	ION 11	8MRTH9	4MRTH4	HOM 5,6		31
71	ION 11	6MRTH4	4MRTH6	HOM 4,5	MKB 5,6	27
	ION 11	8MRTH9	6MRTH6	HOM 4,5	MKB 5,6	36
72	ION 3	4MRTH5	5MRTH9	HOM 3,4	MKB 3,9	15
	ION 3	5MRTH6	6MRTH9	HOM 3,4	MKB 3,9	19
	ION 3	7MRTH8	8MRTH9	HOM 3,4	MKB 3,9	22
73	ION 3	4MRTH10	6MRTH5	HOM 3,4		10
	ION 3	4MRTH5	HOM 3,4			13
85	ION 11	8MRTH9	5MRTH5	HOM 3,4	MKB 5,4	35
86	ION 3	HOM 4,5	MKB 3,4			4
	ION 11	6MRTH4	4MRTH9	HOM 3,4		28
	ION 11	8MRTH9	HOM 3,4			30
	ION 11	8MRTH9	4MRTH2	HOM 3,4		33
87	ION 3	5MRTH6	HOM 4,5			17
	ION 3	4MRTH10	7MRTH6	HOM 4,5		12
100	ION 3	4MRTH10	5MRTH4	HOM 5,6	MKB 4,5	8
	ION 3	5MRTH6	4MRTH4	HOM 5,6	MKB 4,5	18
	ION 3	7MRTH8	6MRTH4	HOM 5,6	MKB 4,5	21
114	ION 3	4MRTH5	HOM 6,7	MKB 5,6		14
	ION 3	4MRTH10	6MRTH5	HOM 6,7	MKB 5,6	11
115	ION 3	7MRTH8	HOM 6,7			20
128	ION 3	4MRTH10	5MRTH4	HOM 3,9	MKB 3,4	7
	ION 3	4MRTH10	5MRTH2	HOM 3,9	MKB 2,3	9
	ION 3	4MRTH1	5MRTH4	HOM 2,3	MKB 3,4	16
	ION 11	8MRTH9	4MRTH4	HOM 3,9	MKB 3,4	32
129	ION 3	4MRTH10	HOM 3,9			6
142	ION 3	HOM 1,2	MKB 2,3			2
	ION 11	HOM 7,8	MKB 7,11			24
156	ION 3	HOM 2,2′	MKB 2,3			3
	ION 3	HOM 4,4′	MKB 3,4			5
157	ION 3					1
($M^{+\cdot}$)	ION 11					23

As can be seen from Table 2, the program proposed 35 fragmentation mechanisms for the formation of the 16 aforementioned ions. Some of the ions, those with *m/e* 43, 44, 58, 71 and 85, originate, according to the *ION GENERATOR*, only from the molecular ion No. 2. Others, with *m/e* 72, 73, 87, 100, 114, 115, 129 and 156, have been found only through mechanisms starting with the molecular ion No. 1. Finally, those ions with *m/e* 86, 128 and 142 have been explained by the program starting with both molecular ions. Table 2 also shows, for each ion, how many mechanisms involved no hydrogen transfer before cleavage, those which involved the transfer of one hydrogen atom and those which involved the transfer of two hydrogen atoms before bond homolysis occurred to yield the ion.

All of the 35 proposed mechanisms are shown, in shorthand notation, in Table 3 along with the order in which the program presented them. For every mechanism listed in Table 3, a labelling experiment could be designed to substantiate or reject the proposed hydrogen transfer[2]).

Some of the mechanisms proposed by the *ION GENERATOR* will now be illustrated with examples.

α-cleavage next to the nitrogen atom. –

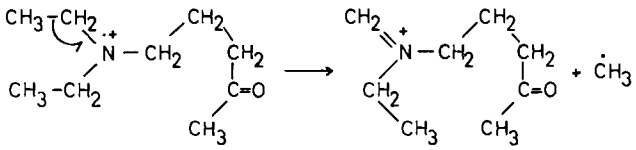
a) *m/e* 142

ION 3 HOM 1,2 MKB 2,3 IMASS 142 INT 3,6% NMASS 15

i.e.: 'ionization on atom No. 3, homolysis between atom No. 1 and atom No. 2, bond formation between atom No. 2 and atom No. 3'. The information concerning the masses of the ionic and neutral species, and the intensity of the corresponding peak found in the mass spectrum are self explanatory.

The shorthand notation shown above corresponds to the mechanism outlined in Scheme 1. The detailed output shows the following structures:

Scheme 1



m/e 142

IONIC SPECIES: N(+) = – –CH2CH2–CH2–CH2–C– = CH3OCH2–CH3

NEUTRAL SPECIES: C(.)H3

An equivalent mechanism is proposed for the formation of *m/e* 142 by α-cleavage. It involves loss of carbon atom No. 10 instead of carbon atom No. 1. As was mentioned before, whenever two mechanisms proposed by the program are equivalent, only one of them is retained in the list given in Table 3.

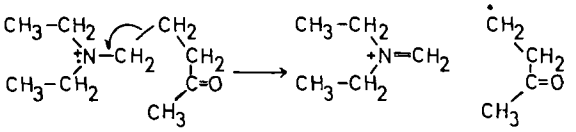
b) *m/e* 86

ION 3 HOM 4,5 MKB 3,4 IMASS 86 INT 100% NMASS 71

[2]) For some of the mechanisms with double hydrogen transfer, labelling experiments could only verify one of the hydrogen transfers.

This mechanism is shown in Scheme 2. The following structures are shown in the output:

Scheme 2



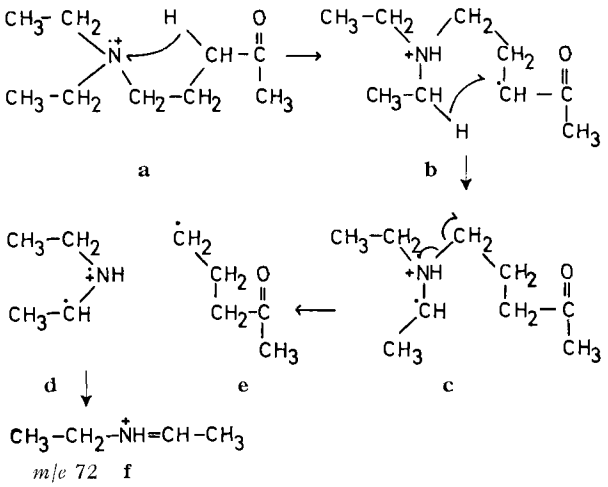
m/e 86

IONIC SPECIES: N(+)– = –CH2–CH3CH2CH2–CH3

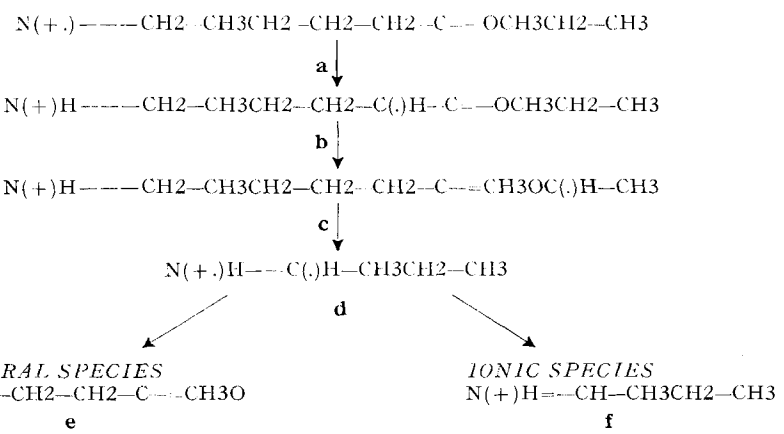
NEUTRAL SPECIES: C(.)H2–CH2–C = –OCH3

Cleavage of molecular ion No. 1 with transfer of hydrogen atoms. – An example in which two consecutive transfers of hydrogen atoms to a radical site occur before a

Scheme 3



m/e 72 **f**



neutral fragment is expelled is afforded by the mechanism proposed for the formation of *m/e* 72.

ION 3 5MRTH6 6MRTH9 HOM 3,4 MKB 3,9 IMASS 72 INT 3,4% NMASS 85

i.e. 'ionization on atom No. 3, transfer of a hydrogen atom from atom No. 6 *via* a five-membered transition state, transfer of a hydrogen atom from atom No. 9 *via* a six-membered transition state, bond homolysis between atom No. 3 and atom No. 4, bond formation between atom No. 3 and atom No. 9'.

The corresponding conventional way of presenting that sequence of operations is illustrated in Scheme 3. For that sequence the structures depicted in Scheme 3 (**a** to **f**) are printed by the program as follows.

Fragmentation starting with molecular ion No. 2. – The two α-cleavages next to the carbonyl function are the only mechanisms without hydrogen transfer proposed by the *ION GENERATOR* for the fragmentation of molecular ion No. 2.

a) *m/e* 43

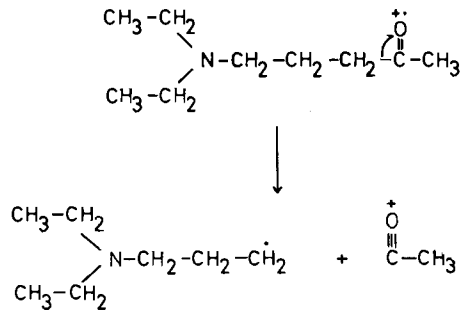
ION 11 HOM 6,7 MKB 7,11 IMASS 43 INT 52,8% NMASS 114

IONIC SPECIES: C = -O(+)CH3

NEUTRAL SPECIES: C(.)H2-CH2-CH2-N--CH2-CH3CH2-CH3

This corresponds to the mechanism depicted in Scheme 4.

Scheme 4



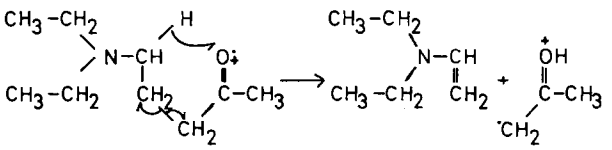
m/e 43

Cleavage on the other side of the carbonyl function was also proposed to yield *m/e* 142. The abbreviated notation for that fragmentation is:

ION 11 HOM 7,8 MKB 7,11 IMASS 142 INT 3,6% NMASS 15

b) *m/e* 58

Scheme 5



m/e 58

The *McLafferty* rearrangement shown in Scheme 5, which leads to *m/e* 58, was proposed in the following way:

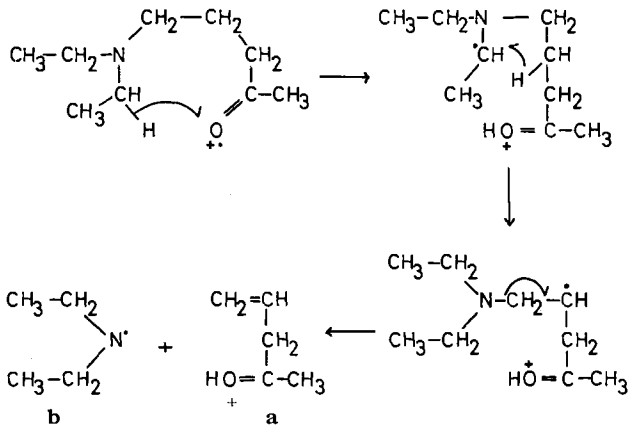
ION 11 6MRTH4 HOM 5,6 IMASS 58 INT 26,4% NMASS 99

IONIC SPECIES: O(+)H = C--CH3C(.)H2

NEUTRAL SPECIES: CH2 = CH–N--CH2–CH3CH2–CH3

As can be seen from Table 3, the program proposed only one mechanism for the formation of *m/e* 85. The fragmentation was visualized as starting from the molecular

Scheme 6



m/e 85

ion No. 2 to yield ion **a** shown in Scheme 6. The abbreviated notation corresponding to the mechanism illustrated in Scheme 6 and the structures of the ionic and neutral species are:

ION 11 8MRTH9 5MRTH5 HOM 3,4 MKB 4,5 IMASS 85 INT 30,7% NMASS 72

IONIC SPECIES: O(+)H = C--CH3CH2–CH = CH2
(structure **a** in Scheme 6)

NEUTRAL SPECIES: N(.)--CH2–CH3CH2–CH3
(structure **b** in Scheme 6)

A high-resolution measurement showed the signal at *m/e* 85 to be actually a singulet, due to an ion with the elemental composition C_5H_9O.

Table 3 shows also the order in which the ions were generated. The first ion to be created was, as has already been mentioned, the molecular ion No. 1. After that, the program generated all the ions arising from that form of the molecular ion, before building the other form of the molecular ion. Mechanisms which yield the same ion, from the same molecular ion, do not necessarily follow each other as is apparent from Table 3. This is due to the several points of view taken by the program in order to generate *all* plausible mechanisms.

By comparing the actual mass spectrum (Figure 2) of 5-diethylamino-pentan-2-one with the list of the ions shown in Table 2, it can be concluded that most of the important ions were generated. Although 22 of the 35 proposed mechanisms involve a double hydrogen transfer, they are plausible mechanisms and cannot be rejected *a priori*, without disproving them by means of deuterium labelling experiments. We are convinced that the *ION GENERATOR* has the potentiality to discover new mechanisms which have been missed in past studies of mass spectral fragmentation. The next step will be to implement more sophisticated primitive operations and to allow the program to explore any depth in the ionic area.

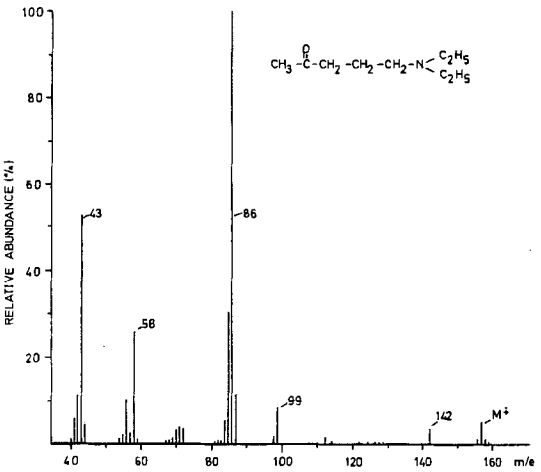


Figure 2: *Mass spectrum of 5-diethylamino-pentan-2-one (70 eV).*

Experimental Part

The computer program was developed for the CDC 3800 computer at the Computer Center of the University of Geneva. It is written in the FORTRAN programming language. To fragment the structure of 5-diethylaminopentan-2-one down to primary ions the computer needed approximately 3 minutes. The low-resolution mass spectrum of **1** was recorded at 70 eV with a *Varian* MAT CH-4 mass spectrometer. High-resolution measurements were performed with a *Varian* MAT SM-1 instrument.

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BIBLIOGRAPHY

[1] *H. Budzikiewicz, C. Djerassi & D. H. Williams*, 'Mass Spectrometry of Organic Compounds', Holden-Day, San Francisco 1967.

[2] *B. G. Buchanan, E. A. Feigenbaum & J. Lederberg*, MEMO AIM-145, Report No. CS-221, Stanford Artificial Intelligence Project, 1971.

[3] *J. Lederberg*, 'Topology of Molecules', in The Mathematical Sciences', M.I.T. Press, Cambridge, Mass. 1969, pp. 37–51.

[4] *B. G. Buchanan, A. M. Duffield & A. V. Robertson*, in 'Mass Spectrometry. Techniques and Applications'. Ed. G.W.A. Milne, Wiley-Interscience, New-York 1971, pp. 121–178.