

Baghdad College of Medical Sciences

5th Class, 2nd Semester

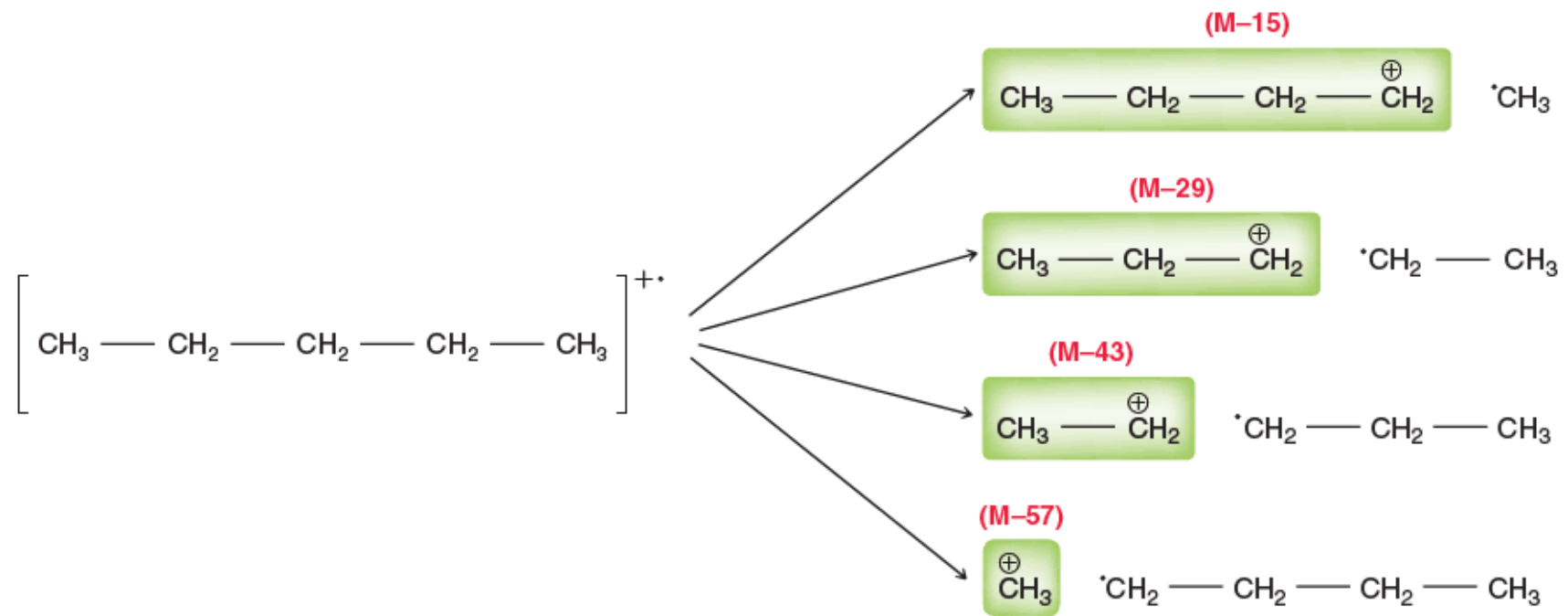
Advanced Pharmaceutical Analysis

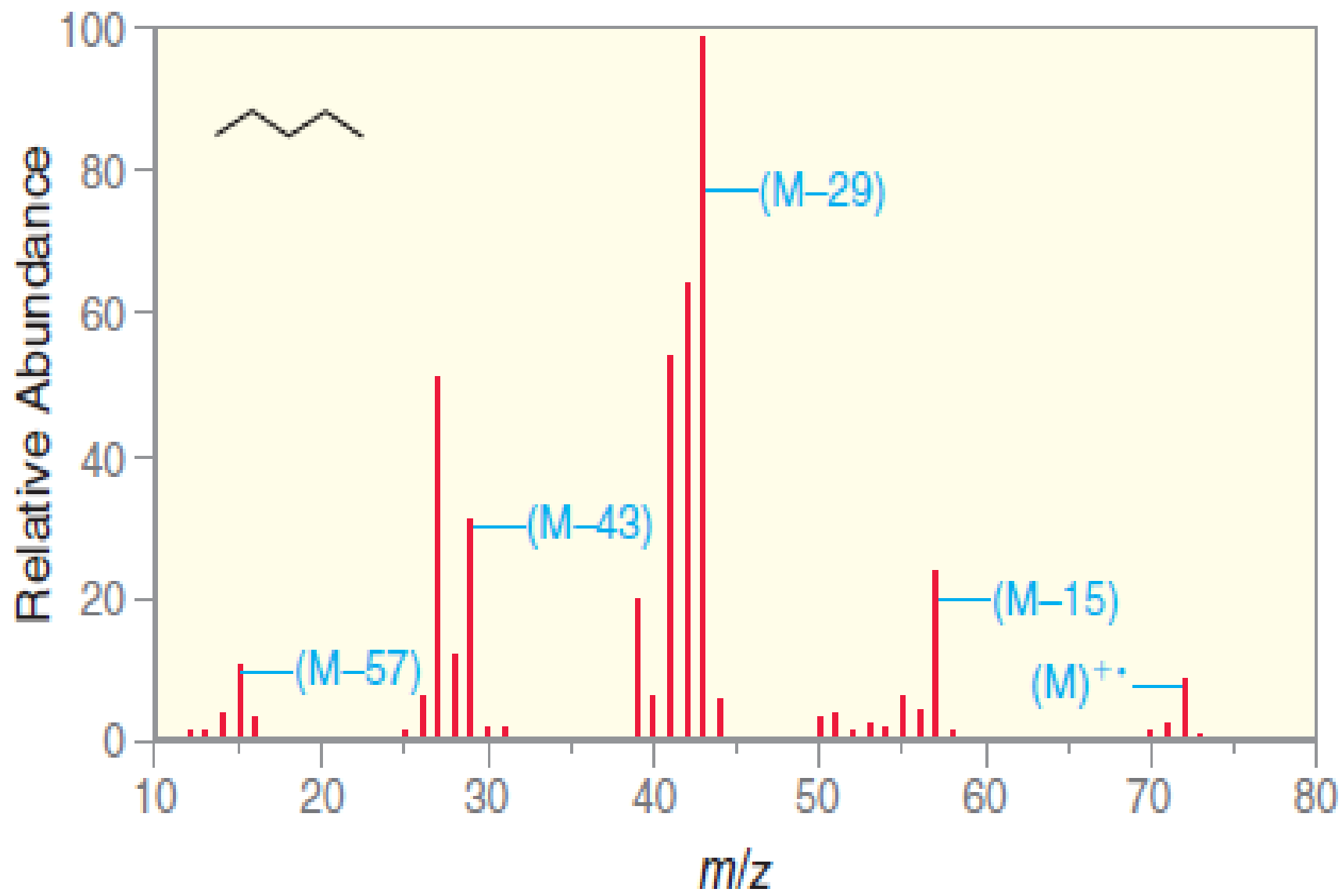
Mass Spectrometry **2nd Lecture**

Ass. lecturer Imad Muneeb

Fragmentation of Alkanes

- Molecular ion peaks are present, possibly with low intensity. The fragmentation pattern contains clusters of peaks 14 mass units apart (which represent loss of $(\text{CH}_2)_n\text{CH}_3$).
- Consider the different ways in which the molecular ion of pentane can fragment.
- Pentane has five carbon atoms connected by a series of four C–C bonds.
- Each of these bonds is susceptible to fragmentation, giving rise to four possible cations.
- Remember that a mass spectrometer does not detect the radical fragments; it only detects the ions.

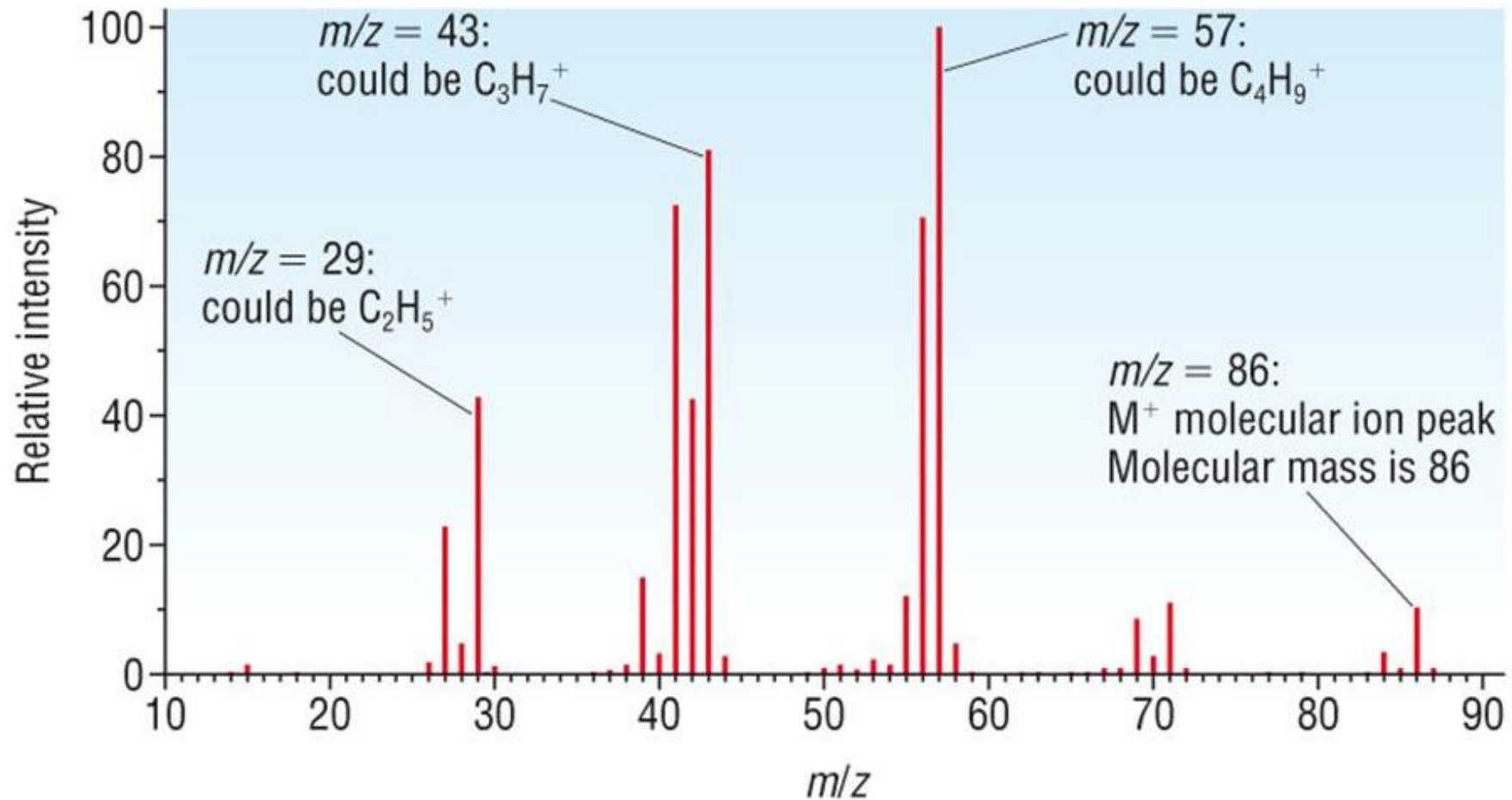




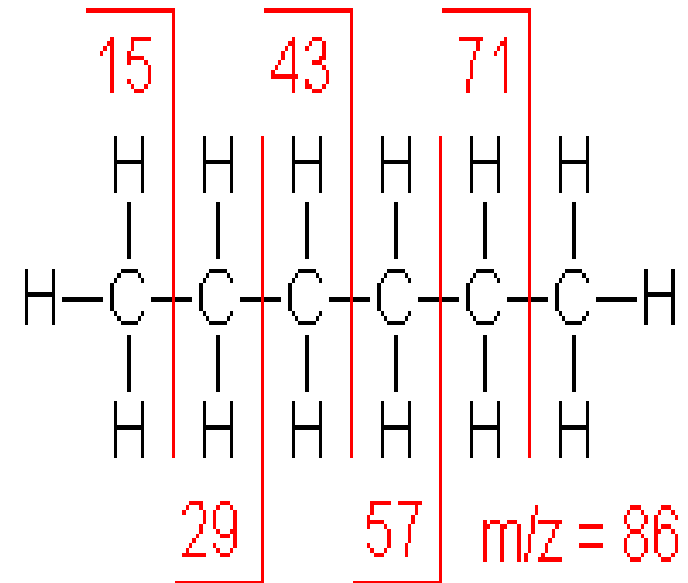
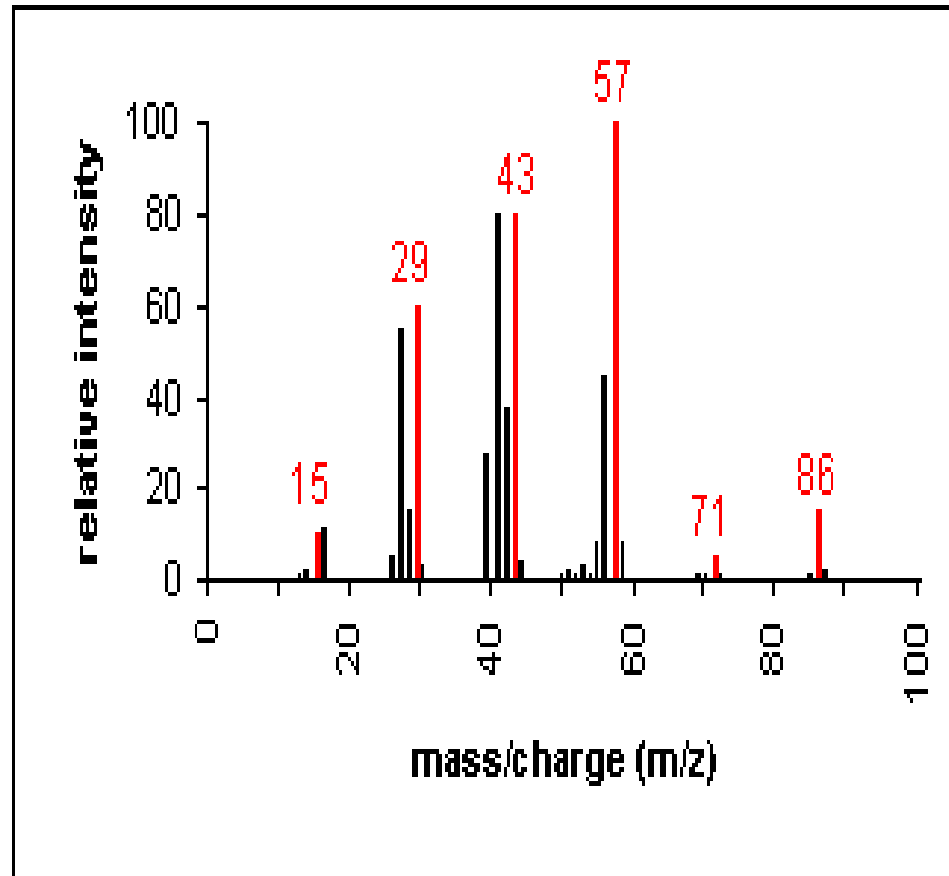
A mass spectrum of pentane.

- The first cation shown is formed from loss of a methyl radical.
- The methyl radical has a mass of 15, so the resulting cation appears as a peak at M-15.
- The second cation is formed from the loss of an ethyl radical (mass 29), so the resulting peak appears at M-29.
- In a similar way, the other two possible cations appear at M-43 and M-57, corresponding with the loss of a propyl radical and butyl radical, respectively.
- All four of these cations can be observed in the spectrum of pentane.

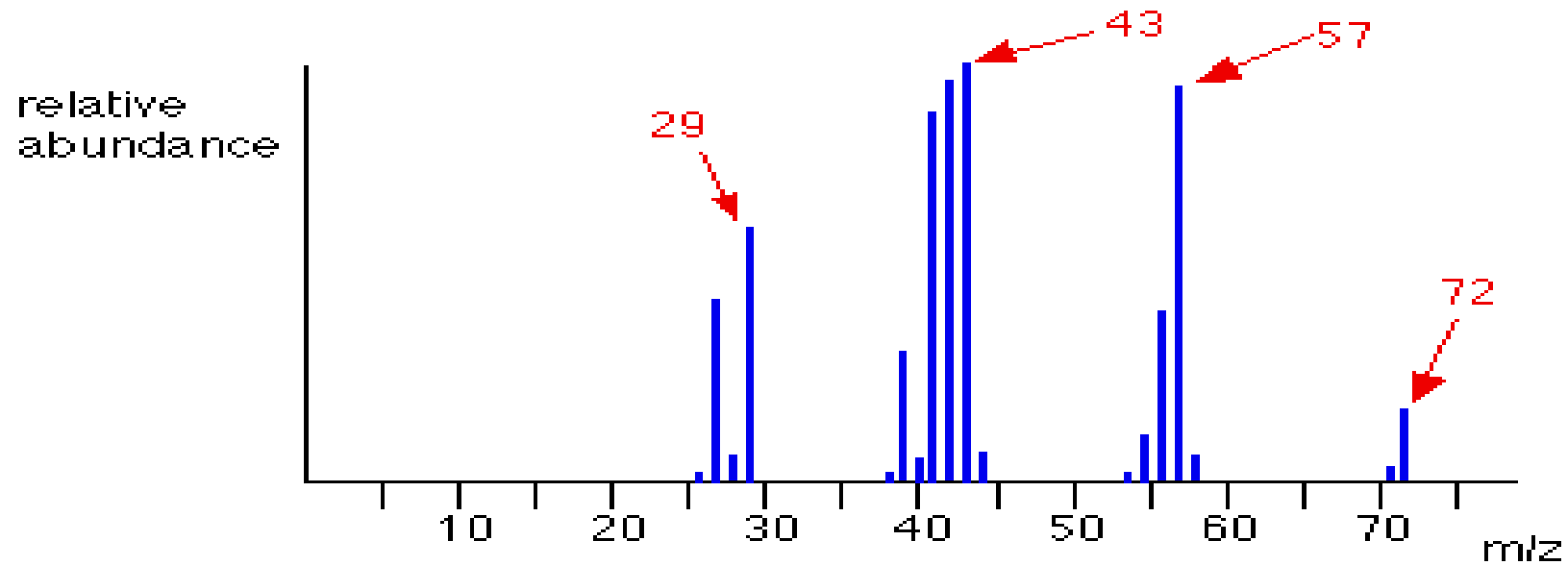
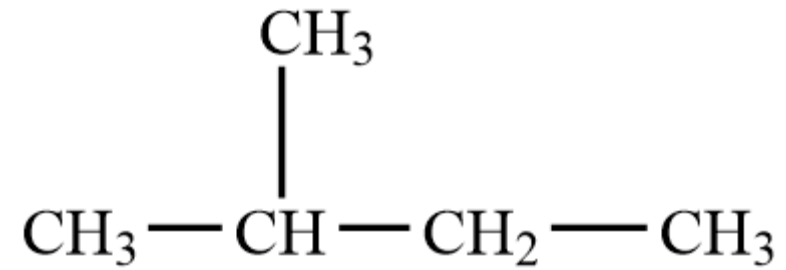
Analyzing the $(M)^+$ Peak Hexane



Hexane (C₆H₁₄) with MW = 86.18



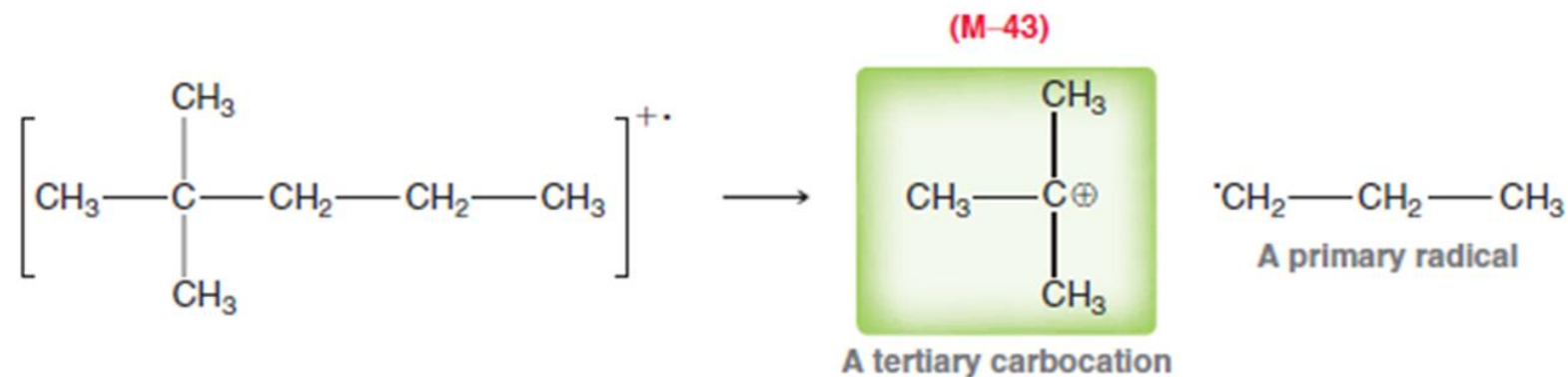
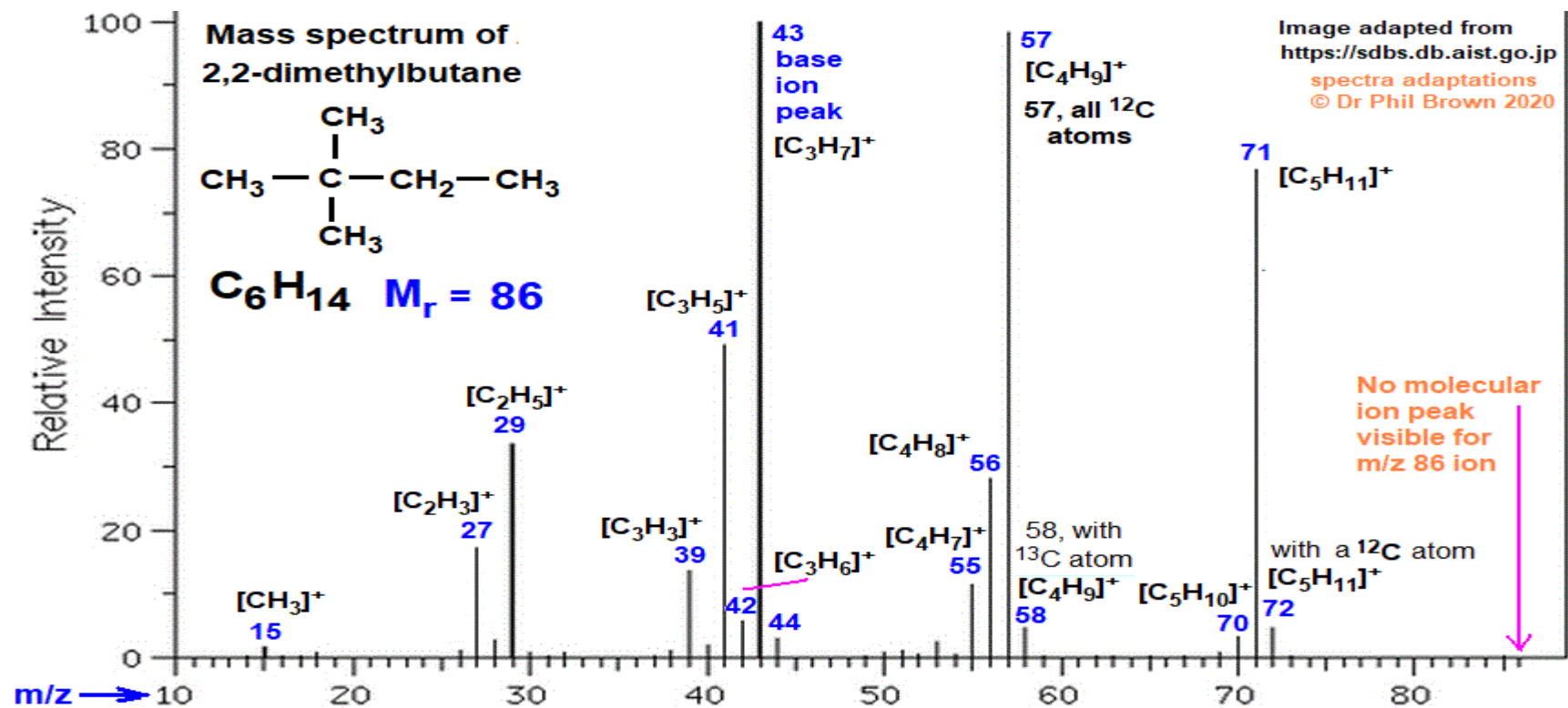
Mass Spectrum of 2-methylbutane



- 2-methylbutane is an isomer of pentane - isomers are molecules with the same molecular formula, but a different spatial arrangement of the atoms.
- H.W. Mention the differences between pentane and 2-methylbutane regarding Molecular Peak Ion and Base Peak Ion with explanations.
- The likelihood of fragmentation increases with the stability of the carbocation formed as well as the stability of the radical that is ejected.
- **Order of stability of carbocations:**
methyl < primary < secondary < tertiary

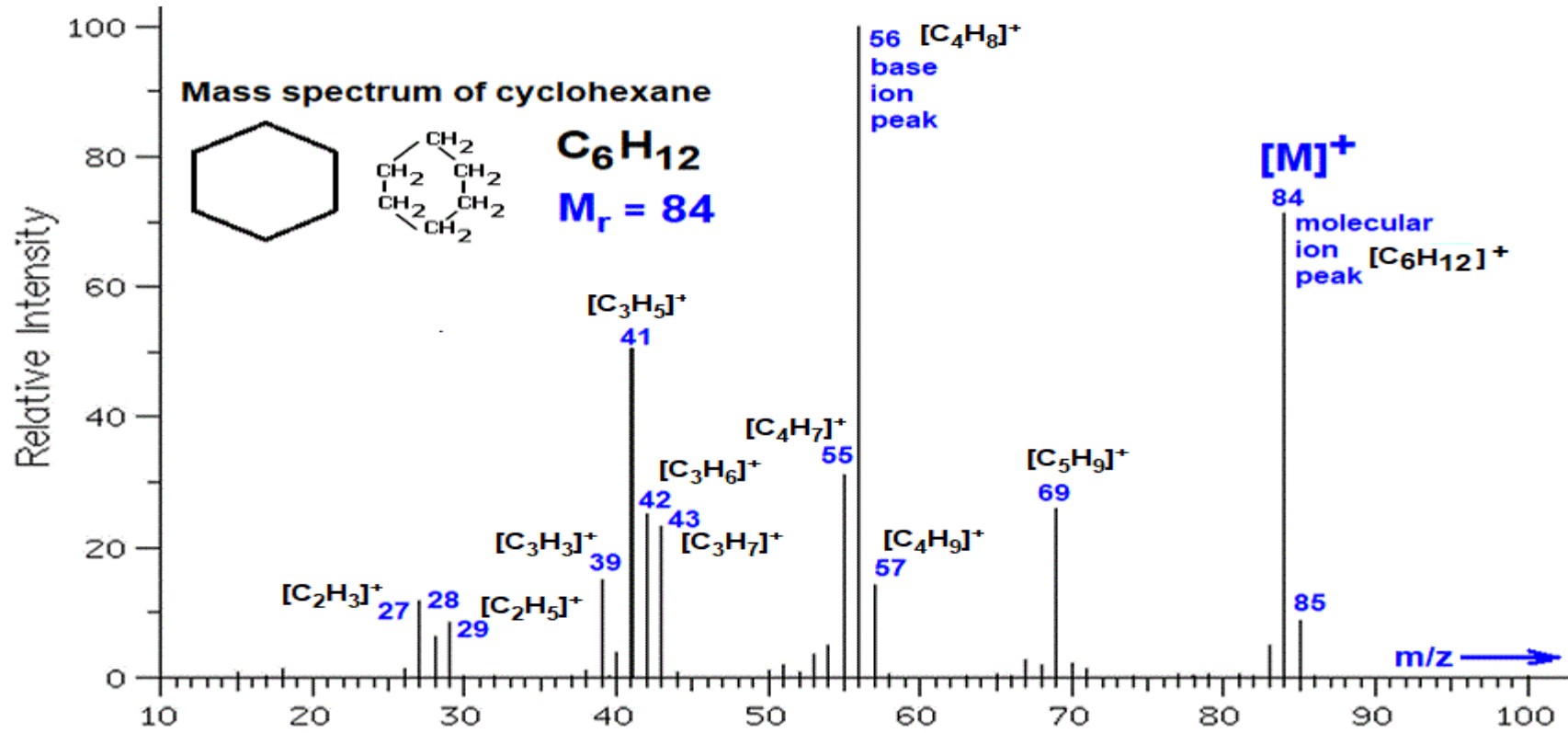
- For example, look again at the various possible carbocations formed by fragmentation of pentane.
- The carbocation corresponding to M-57 is a methyl carbocation, which is less stable than the other possible carbocations (all of which are primary).
- That explains why the peak at M-57 is a fairly small peak in the spectrum.
- In general, fragmentation will occur in all possible locations but will typically favour the formation of the most stable carbocation.

- 2,2-dimethylpentane.



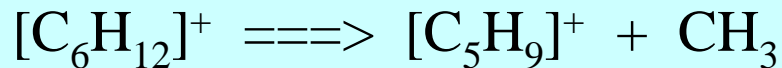
- The most abundant peak in the spectrum of this compound is expected to be at M-43, corresponding with formation of a tertiary carbocation, via loss of a propyl radical.
- A tertiary carbocation can also be produced via loss of a methyl radical (from the left side of the molecular ion above); however, a methyl radical is less stable than a primary radical.
- Certainly, all possible fragmentations are observed under the high-energy conditions employed, but the most abundant peak will generally result from formation of the most stable carbocation via expulsion of the most stable possible radical.
- Therefore, it is generally possible to predict the location of the most abundant peak that is expected in the mass spectrum of a simple alkane or branched alkane.

Cyclohexane mass spectrum fragmentation



m/z value of [fragment] ⁺	69	57	56	55	43	42	41	39	29	27
[molecular fragment] ⁺	$[C_5H_9]^+$	$[C_4H_9]^+$	$[C_4H_8]^+$	$[C_4H_7]^+$	$[C_3H_7]^+$	$[C_3H_6]^+$	$[C_3H_5]^+$	$[C_3H_3]^+$	$[C_2H_5]^+$	$[C_2H_3]^+$

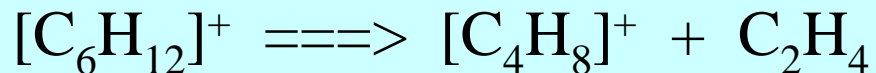
- Formation of m/z 69 ion:



C-C bond scission of the parent molecular ion and proton rearrangement

mass change $84 - 15 = 69$ (M-15 ion peak)

Formation of m/z 56 ion:

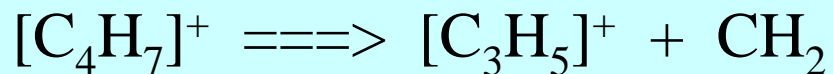


mass change $84 - 28 = 56$, from the molecular ion (M-28 ion peak)

The m/z 56 ion is the **base peak ion**, the most abundant and 'stable' ion fragment. It is formed by the elimination of ethene from the cyclohexane molecular ion.

The m/z values of 83, 69, 55 and 41 are related by the loss of a mass unit of 14 (CH_2) from one fragment ion to the next

Formation of **m/z 41 ion**:

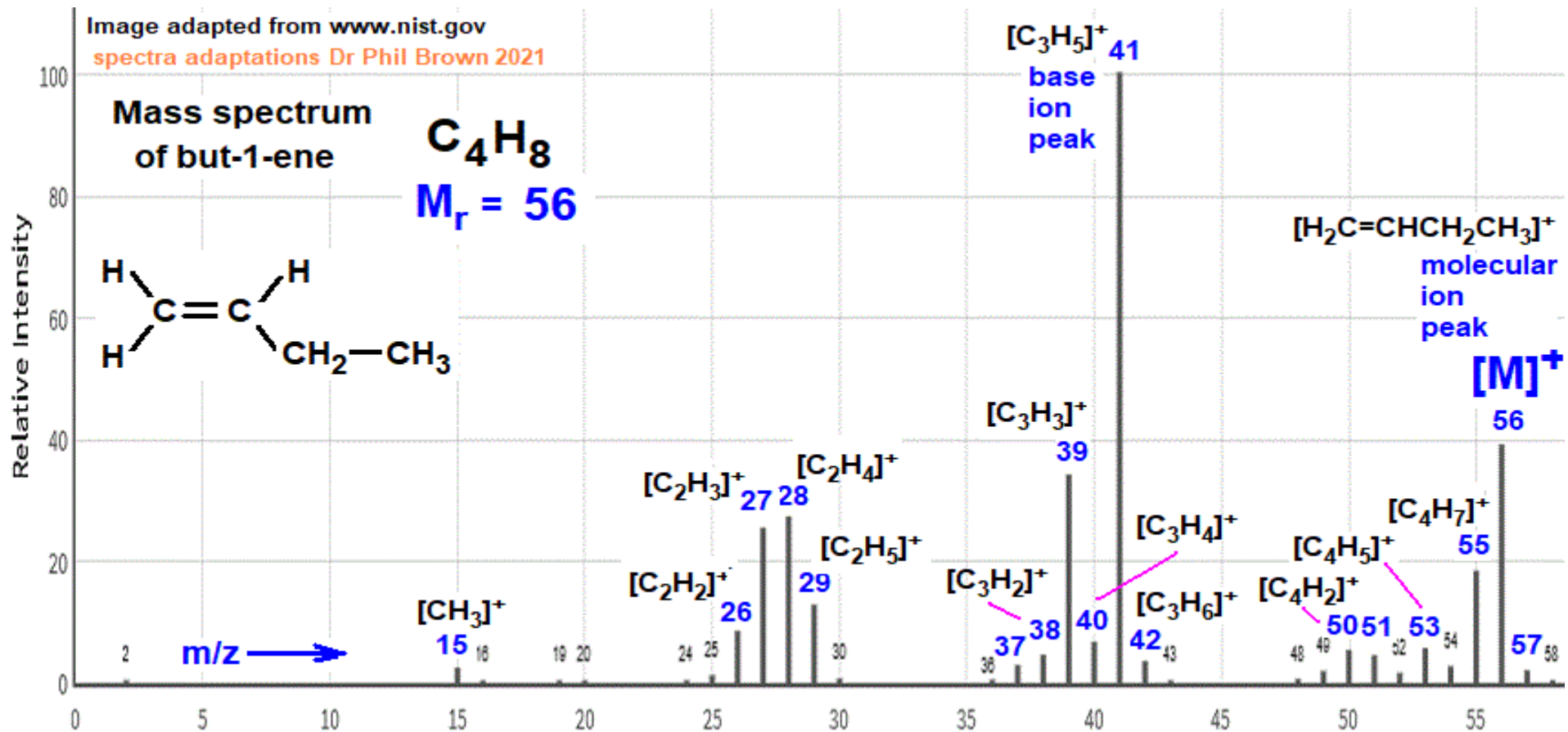


mass change $55 - 14 = 41$

H.W. Mass spectrum of cycloheptane, Molecular peak ion, Base peak ion.

Alkene Fragmentation

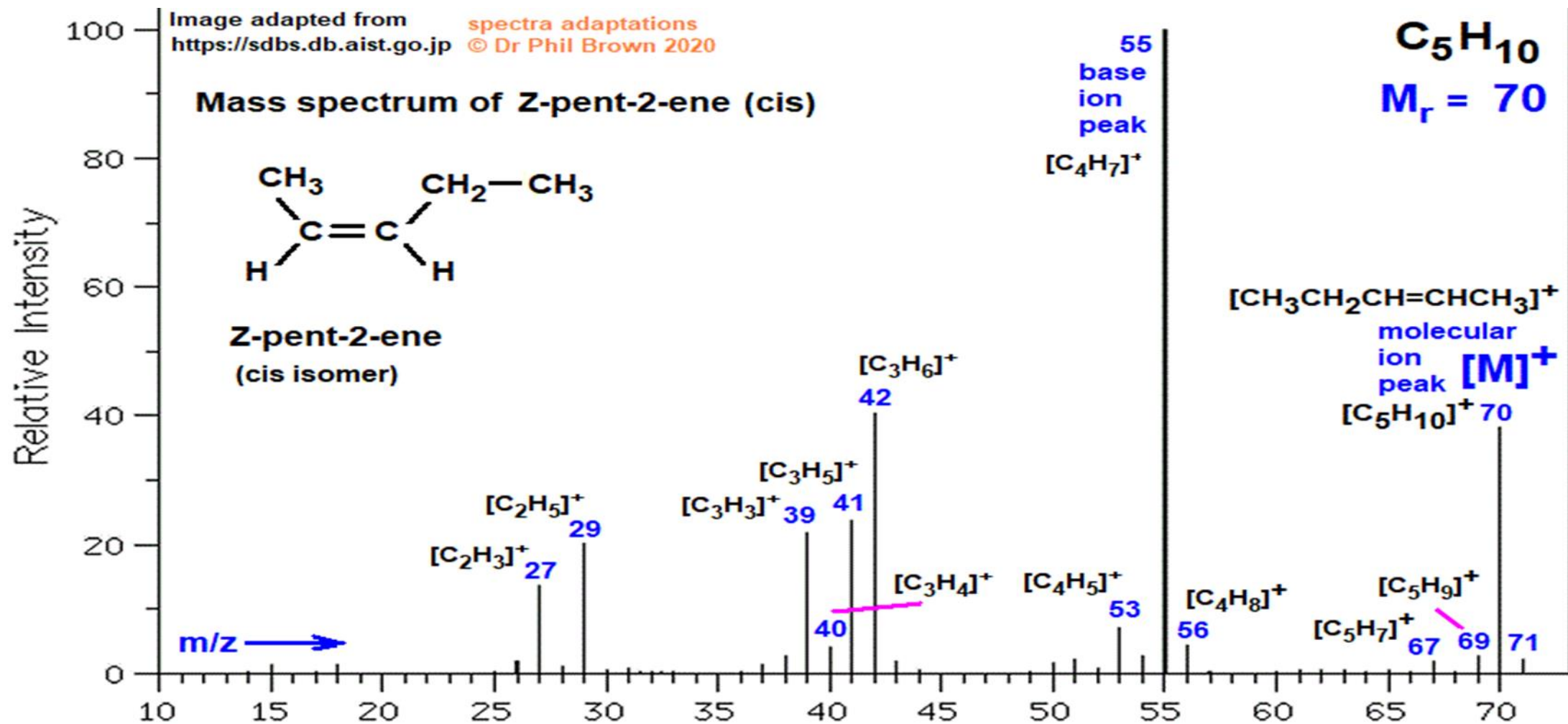
- On ionization, alkenes lose one electron from the unsaturated bond and form stable molecular ions.
- Further fragmentation of alkenes occurs via three different reaction pathways.
 - The most prominent fragmentation is the cleavage at allylic position. The resultant allylic carbocation is resonance stabilized. In the internal alkenes, where there are two choices of allylic cleavage, the cleavage preferentially occurs in a way to generate more substituted alkyl radical as the co-product.
 - Another fragmentation pathway occurs at the carbon-carbon bond adjacent to the unsaturated bond to yield an alkenyl carbocation and a corresponding alkyl radical. The fragmentation preferably occurs in a way to generate a more stable alkyl radical.
- The alkenes possessing γ hydrogen with respect to the unsaturated bond undergo McLafferty rearrangement. The resultant products are an alkene and an alkene radical cation

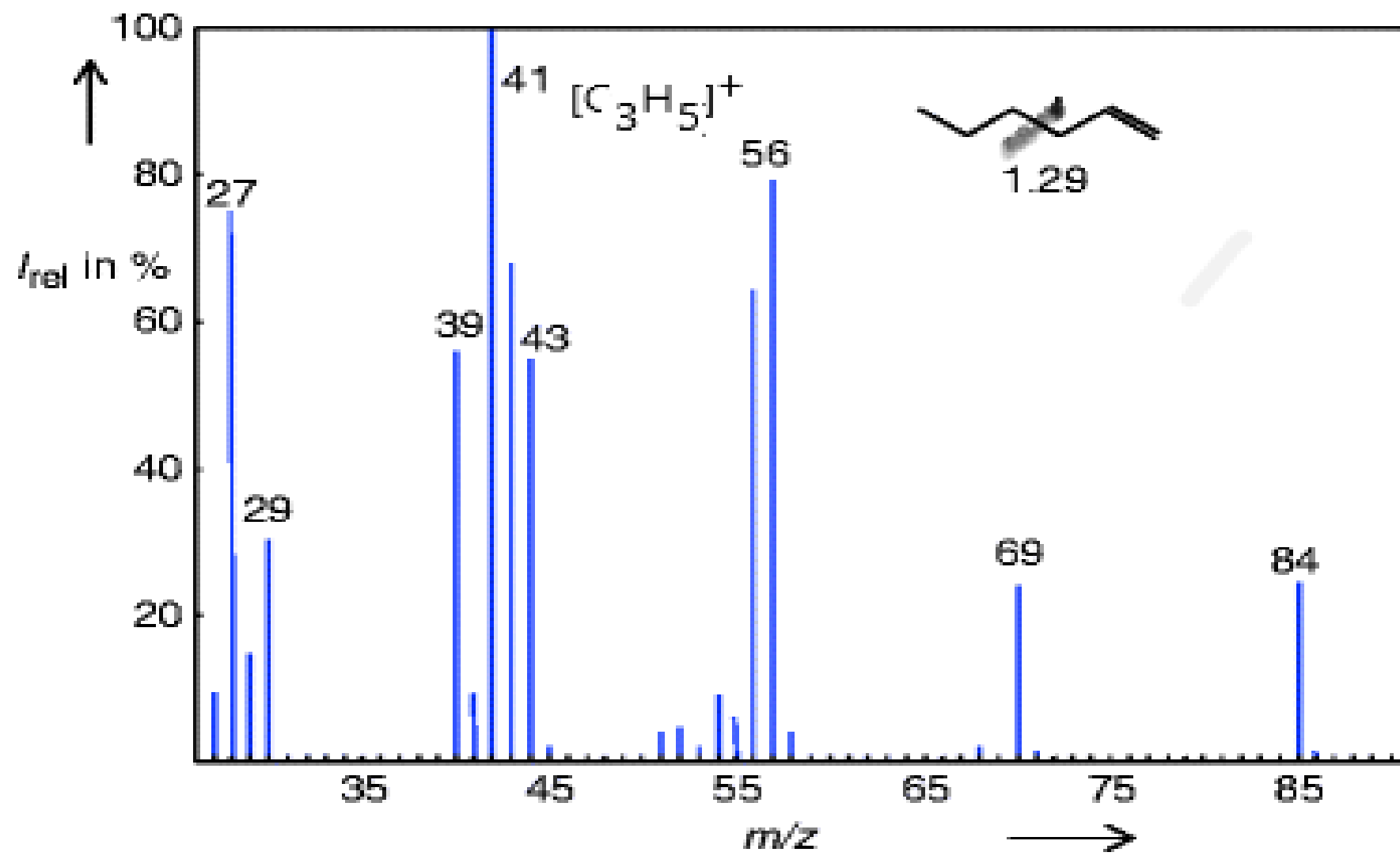


1-butene

$M^+ 56$

Base ion peak 41 (allylic cleavage)





(E) 2-Hexene

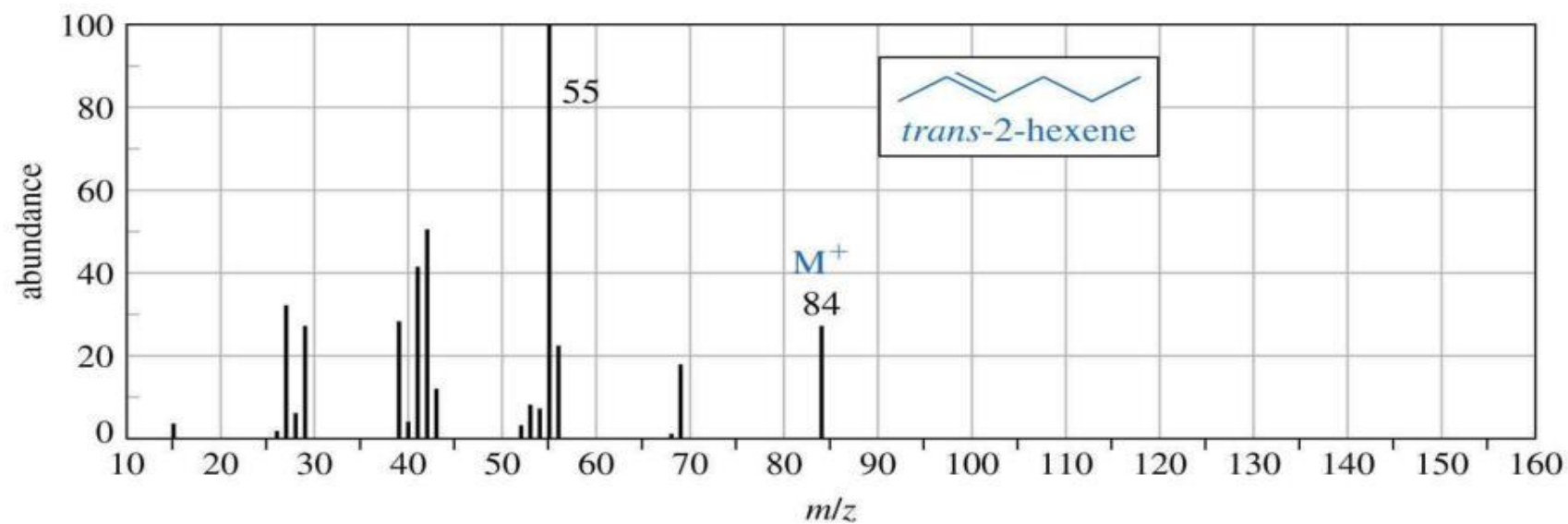
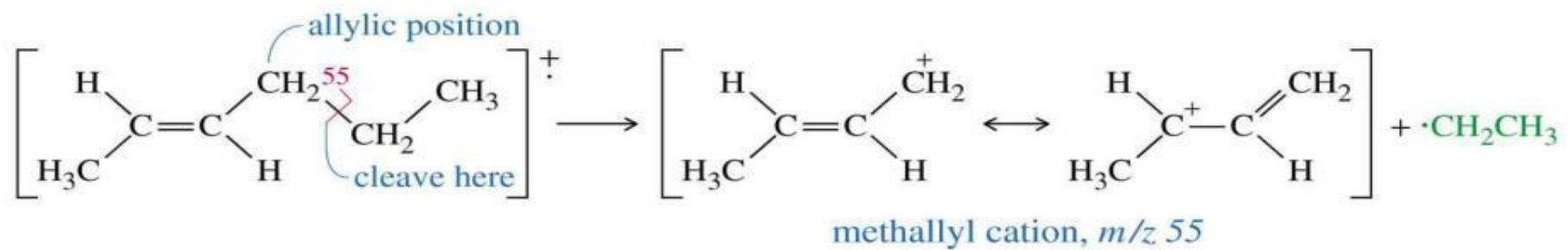
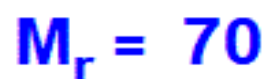
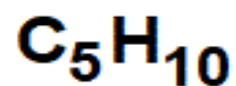
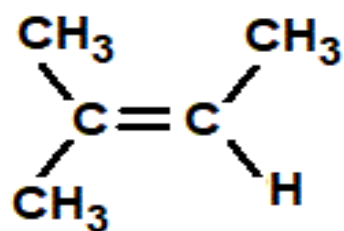
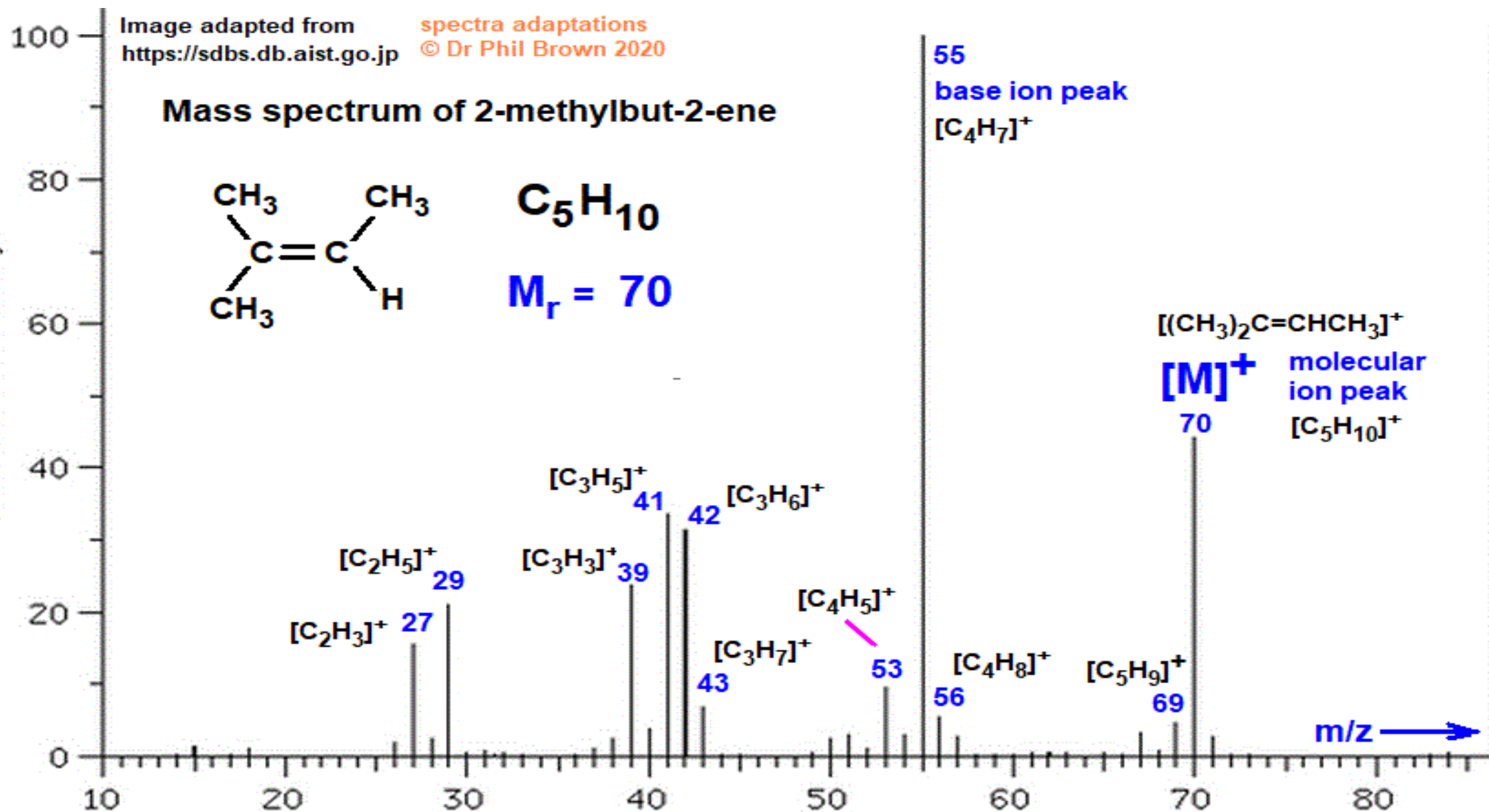


Image adapted from <https://sdfs.db.aist.go.jp> spectra adaptations © Dr Phil Brown 2020

Mass spectrum of 2-methylbut-2-ene



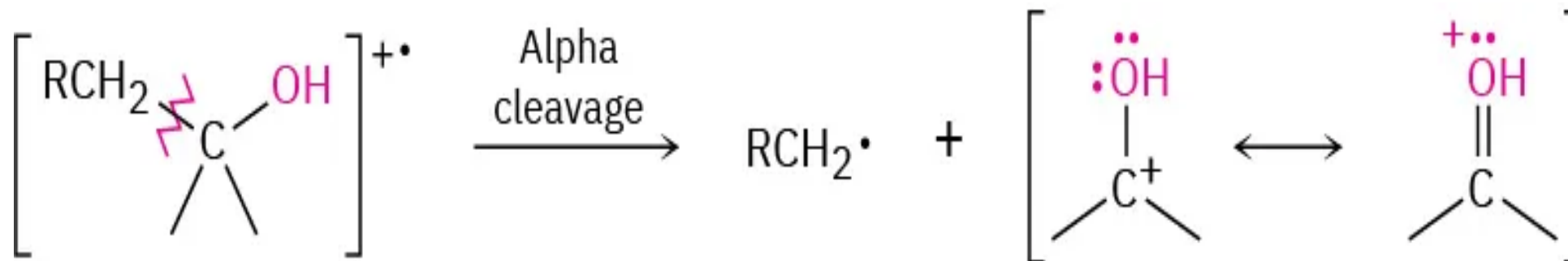
Relative Intensity



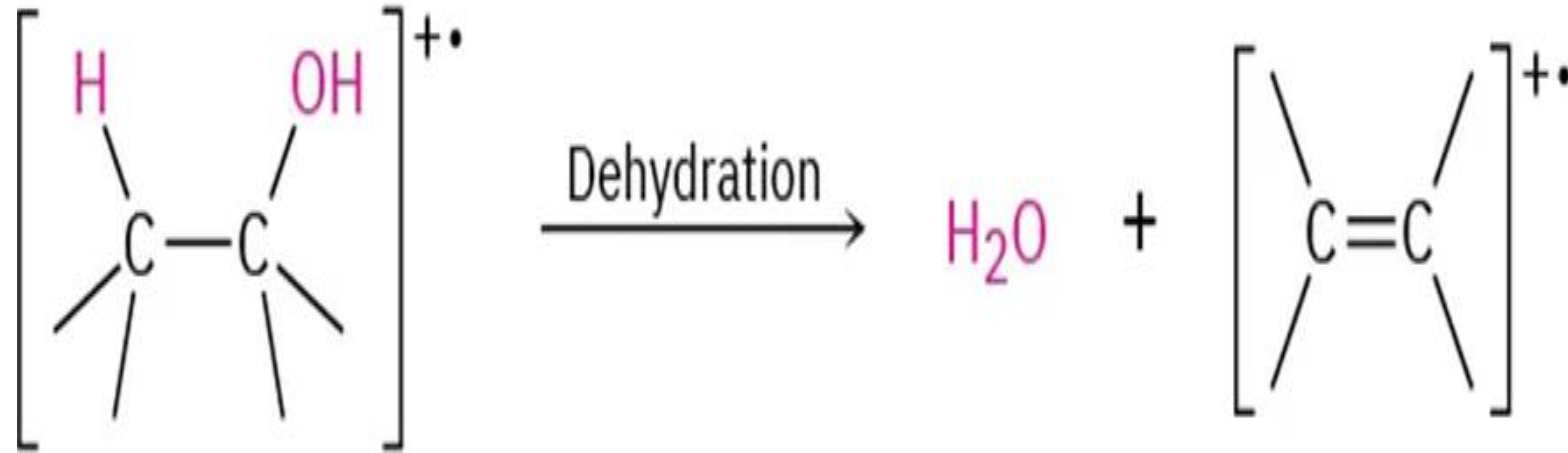
Alcohols fragmentation

Alcohols undergo fragmentation in a mass spectrometer by two pathways: *alpha cleavage* and *dehydration*

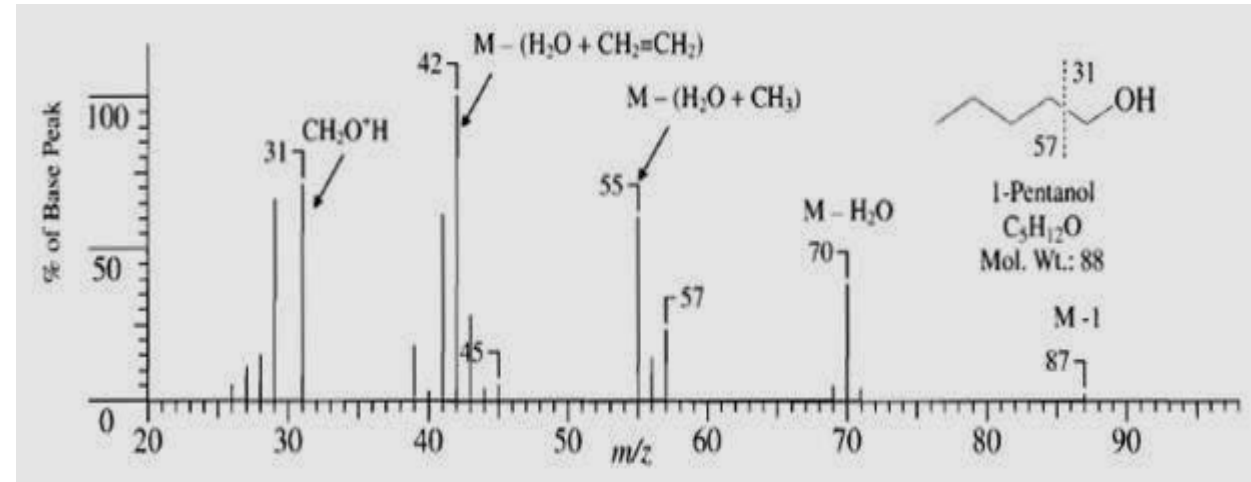
- In the α -cleavage pathway, a C–C bond nearest the hydroxyl group is broken, yielding a larger neutral radical plus a resonance-stabilized, oxygen-containing cation.



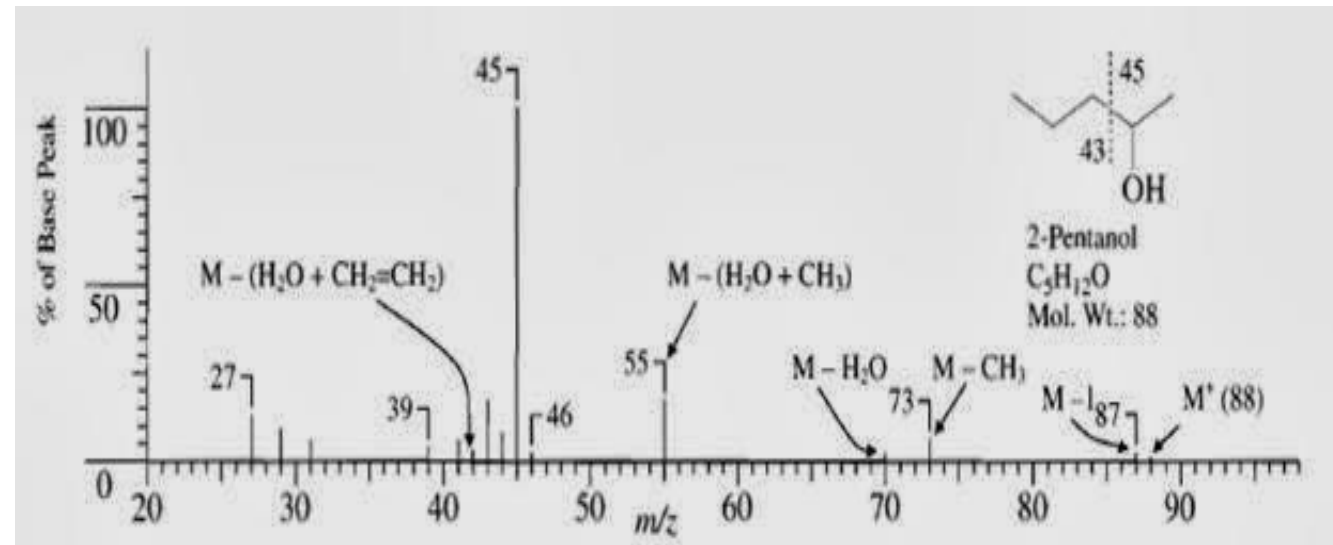
In the dehydration pathway, water is eliminated, yielding an alkene radical cation with a mass 18 less than M^+ . (Small peak)

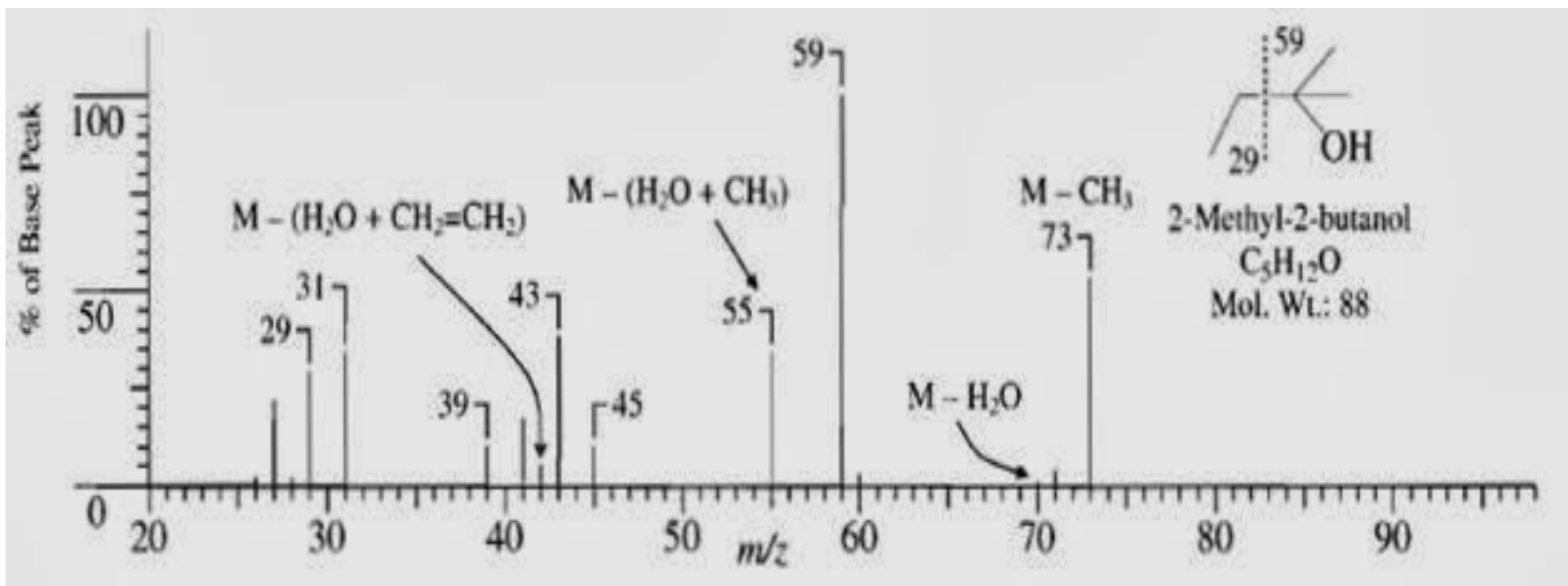


In primary alcohol elimination of water, together with elimination of alkene, accounts for the presence of a base ion peak at $M - (\text{alkene} + \text{H}_2\text{O})$

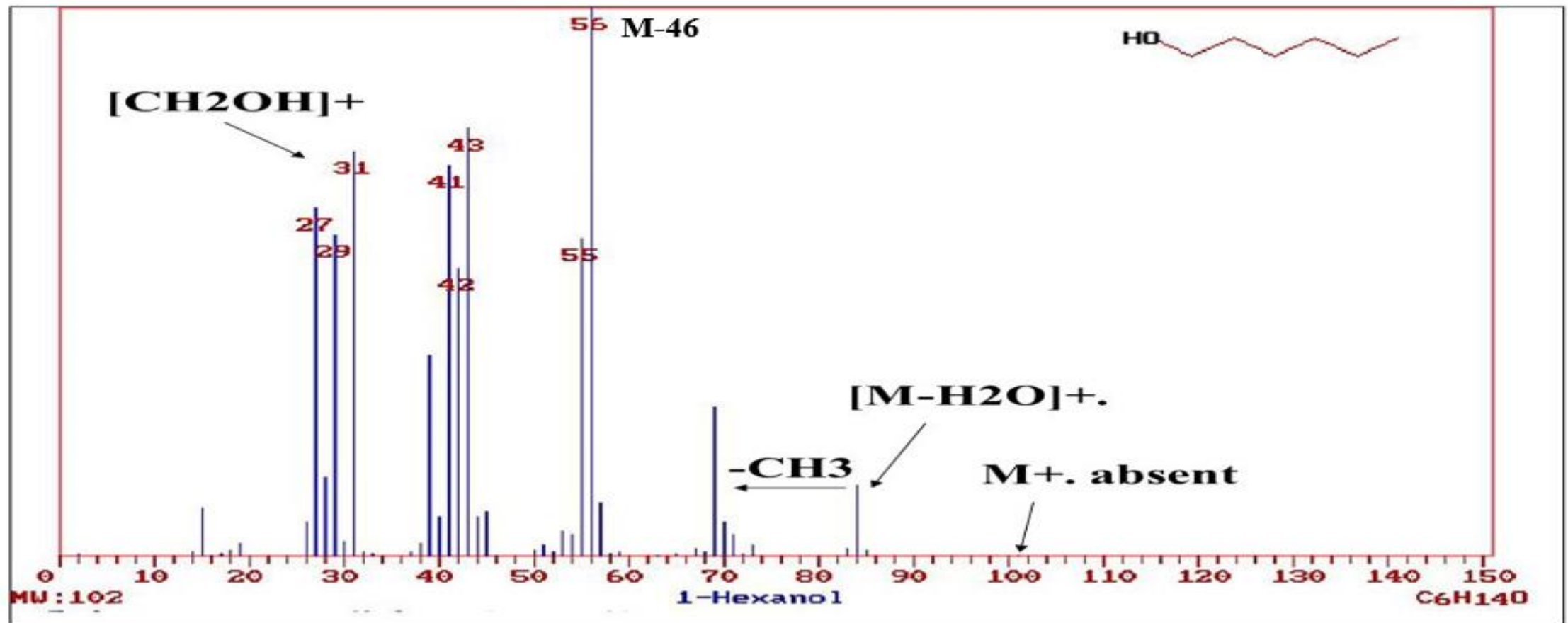


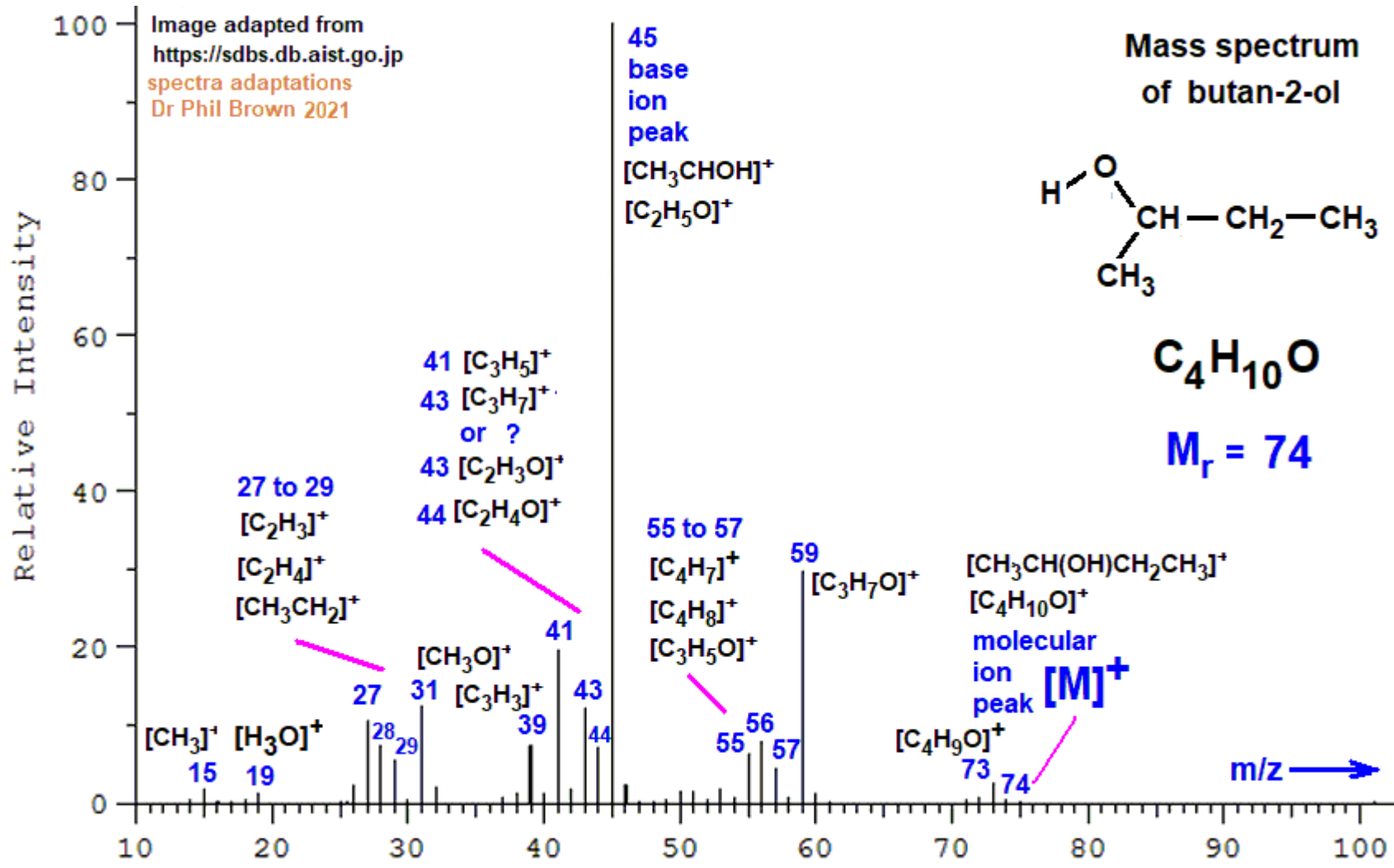
In secondary and tertiary alcohols α -cleavage pathway, a C–C bond nearest the hydroxyl group is broken, yielding a larger neutral radical





1-Hexanol (m/z= 102)



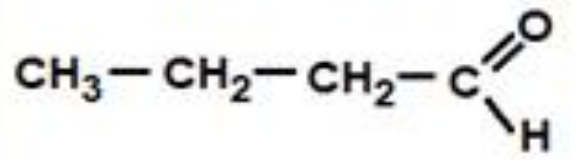


Aldehyde fragmentation

- A common fragmentation pattern observed in ketones is the α cleavage occurring at the carbon–carbon bond at the α position next to the carbonyl group. The α cleavage generates a neutral alkyl radical and an H-C=O^+ or C-H cleavage
- C-C β cleavage and formation of $[\text{CH}_2=\text{CH-OH}]^+$ (rearrangement and H-abstract) giving the base ion peak.

Image adapted from <https://sdfs.db.aist.go.jp>
spectra adaptations Dr Phil Brown 2021

Mass spectrum of butanal

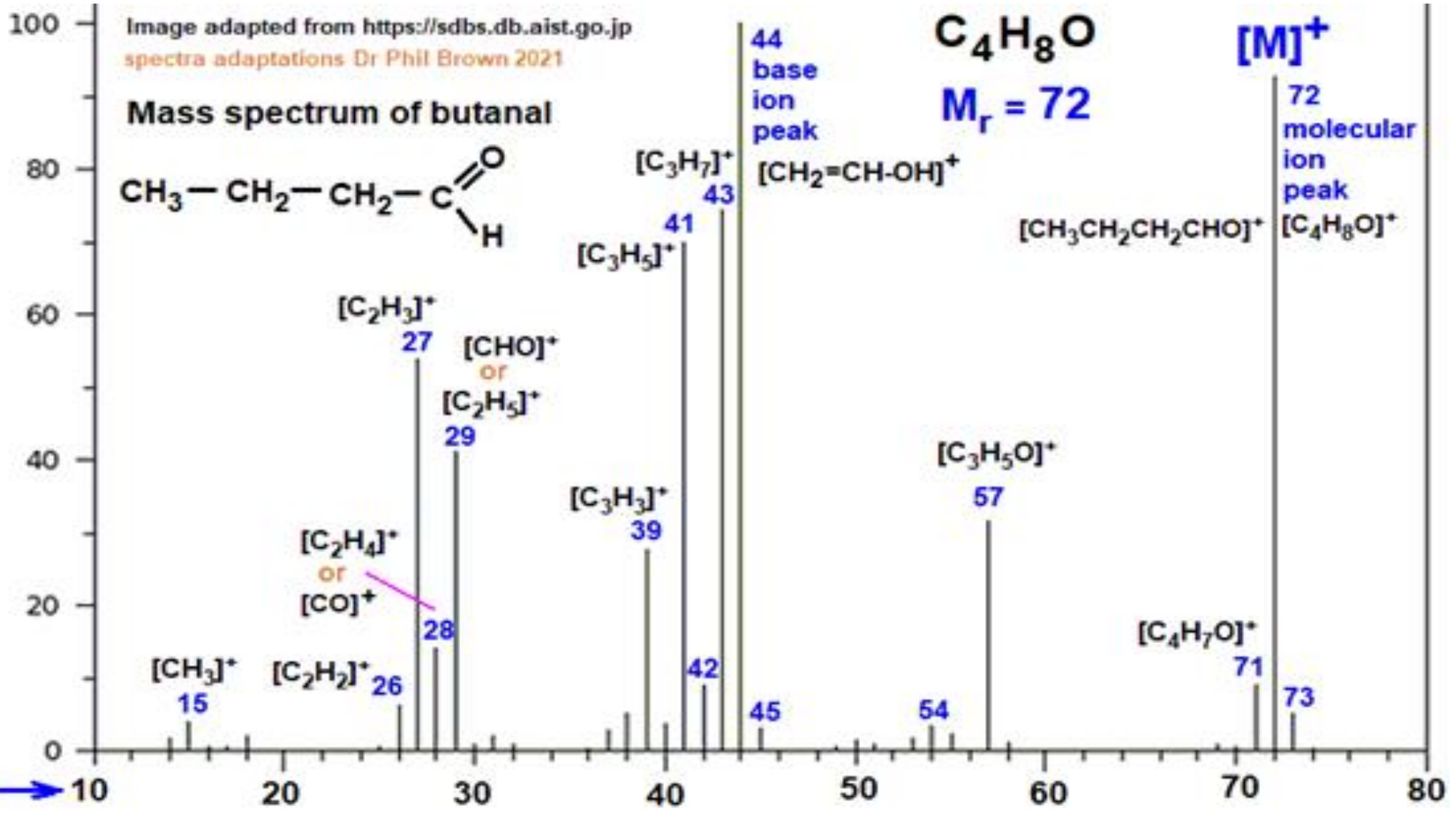


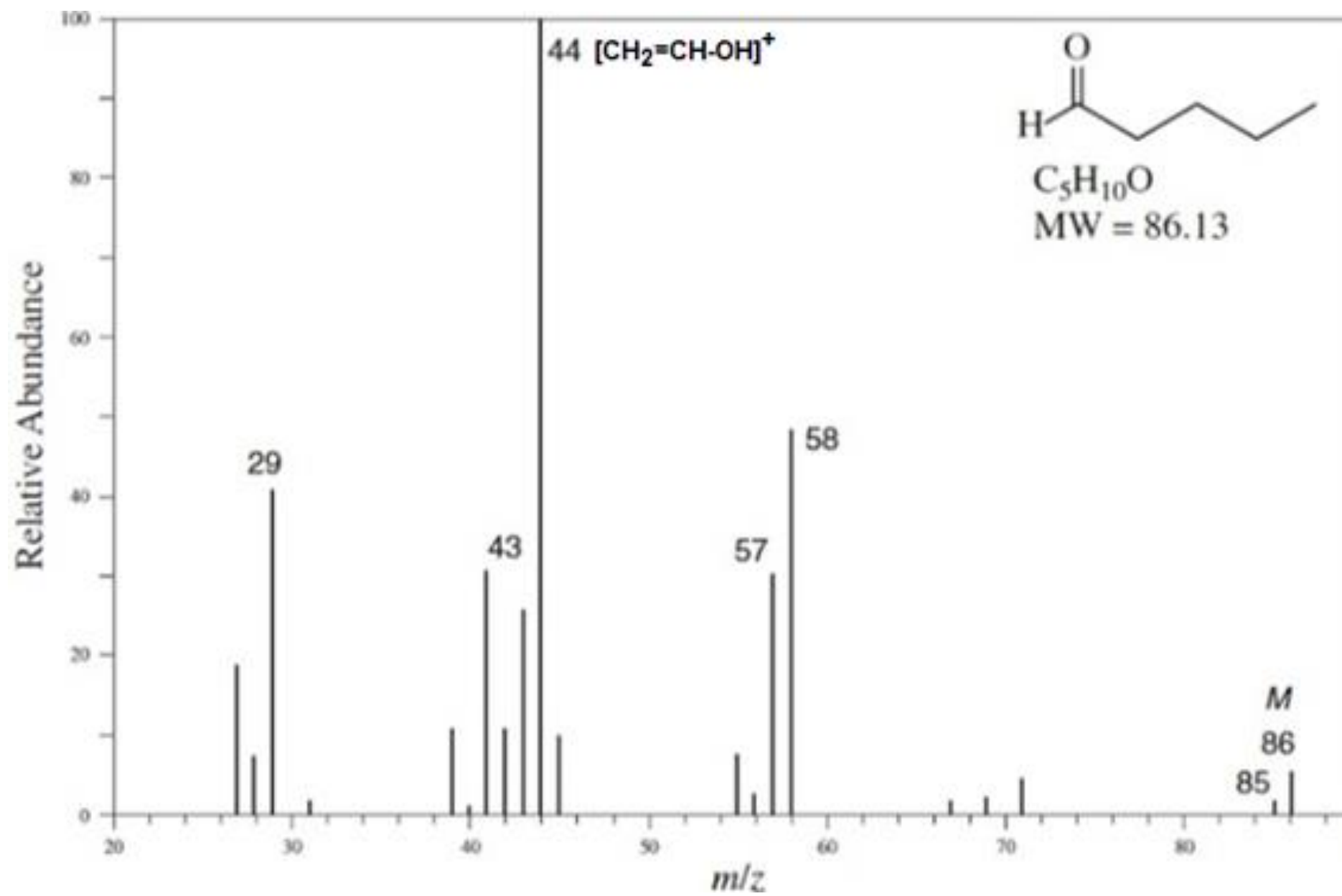
C₄H₈O
M_r = 72

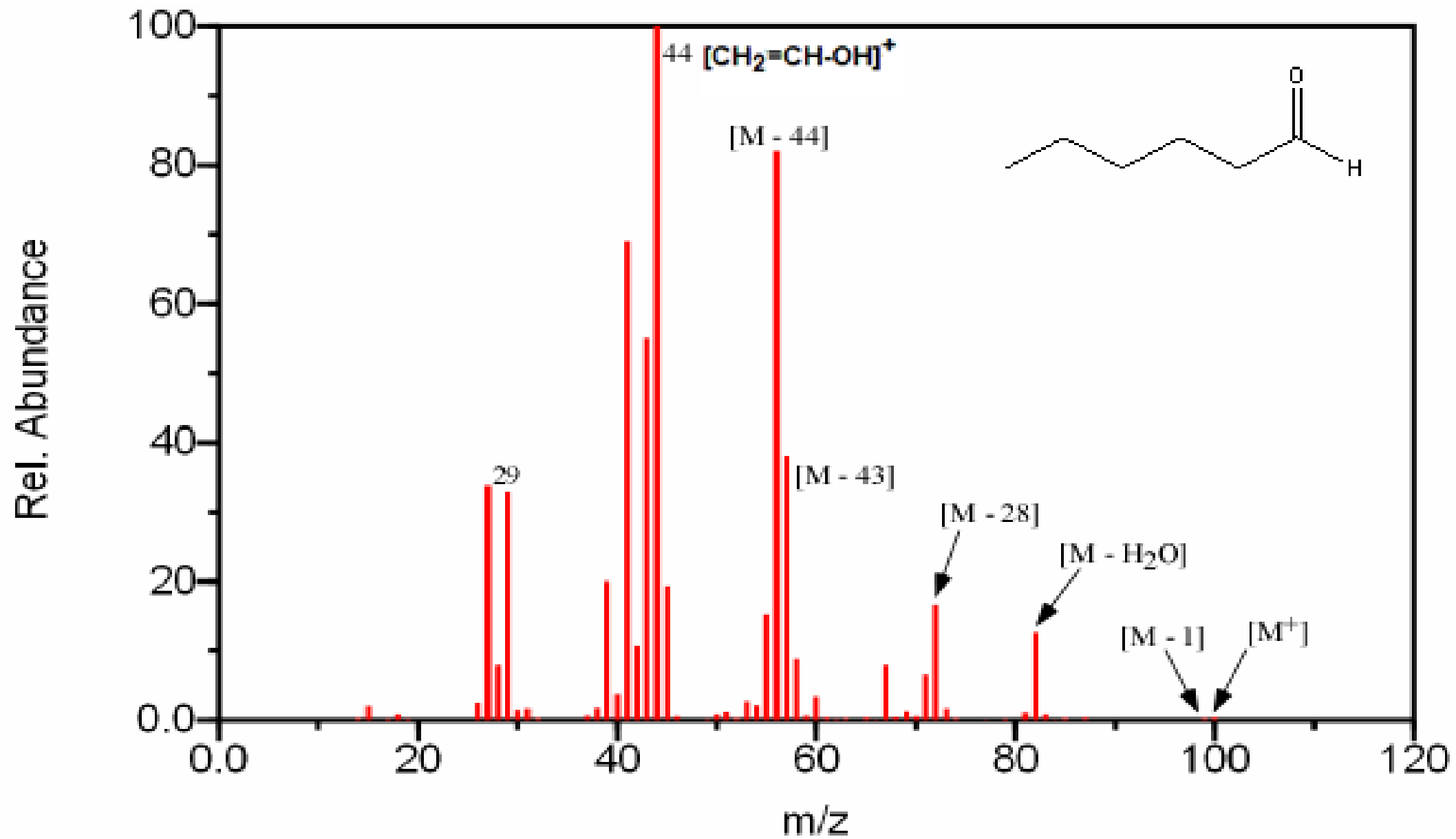
[M]⁺
72
molecular ion peak
[C₄H₈O]⁺

Relative Intensity

m/z →



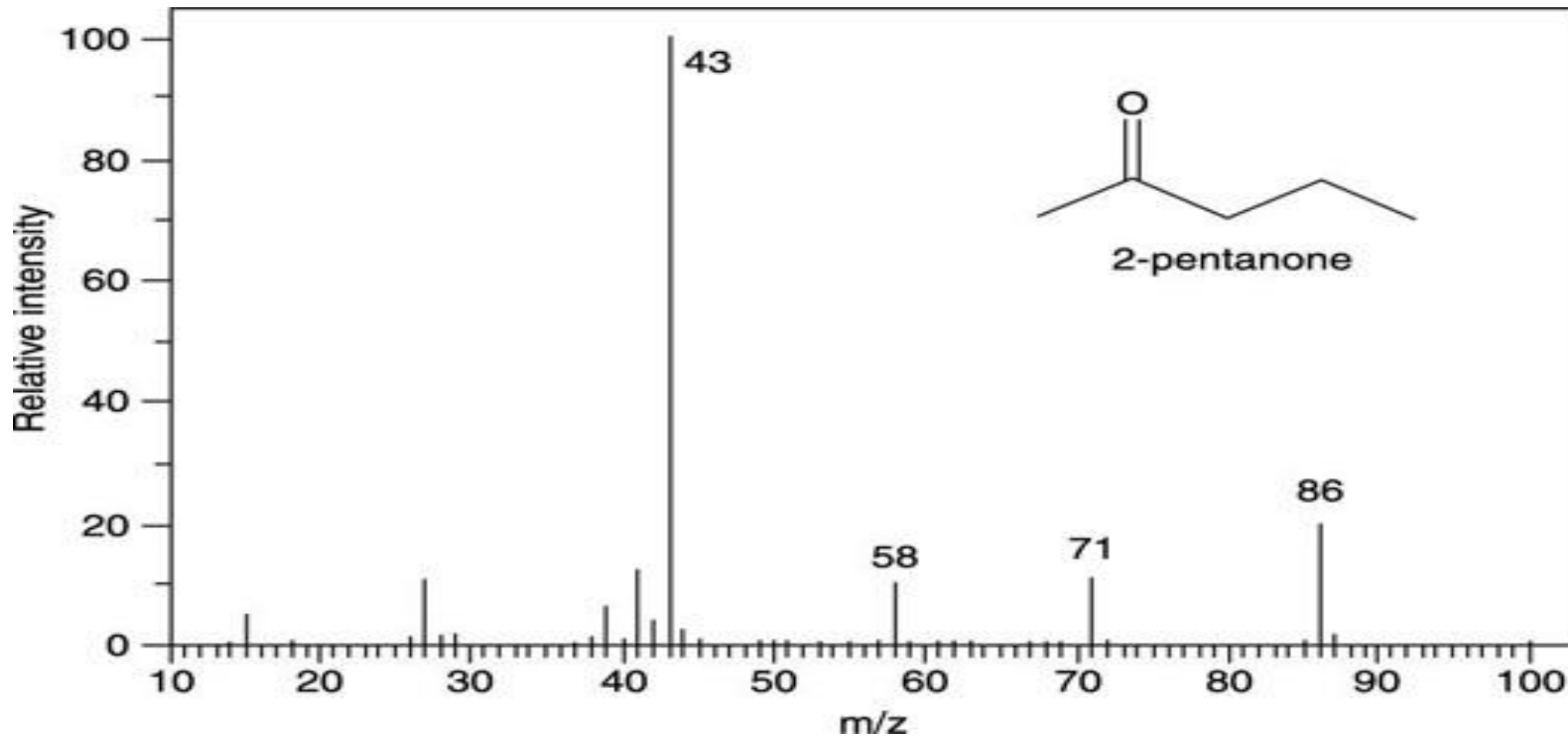




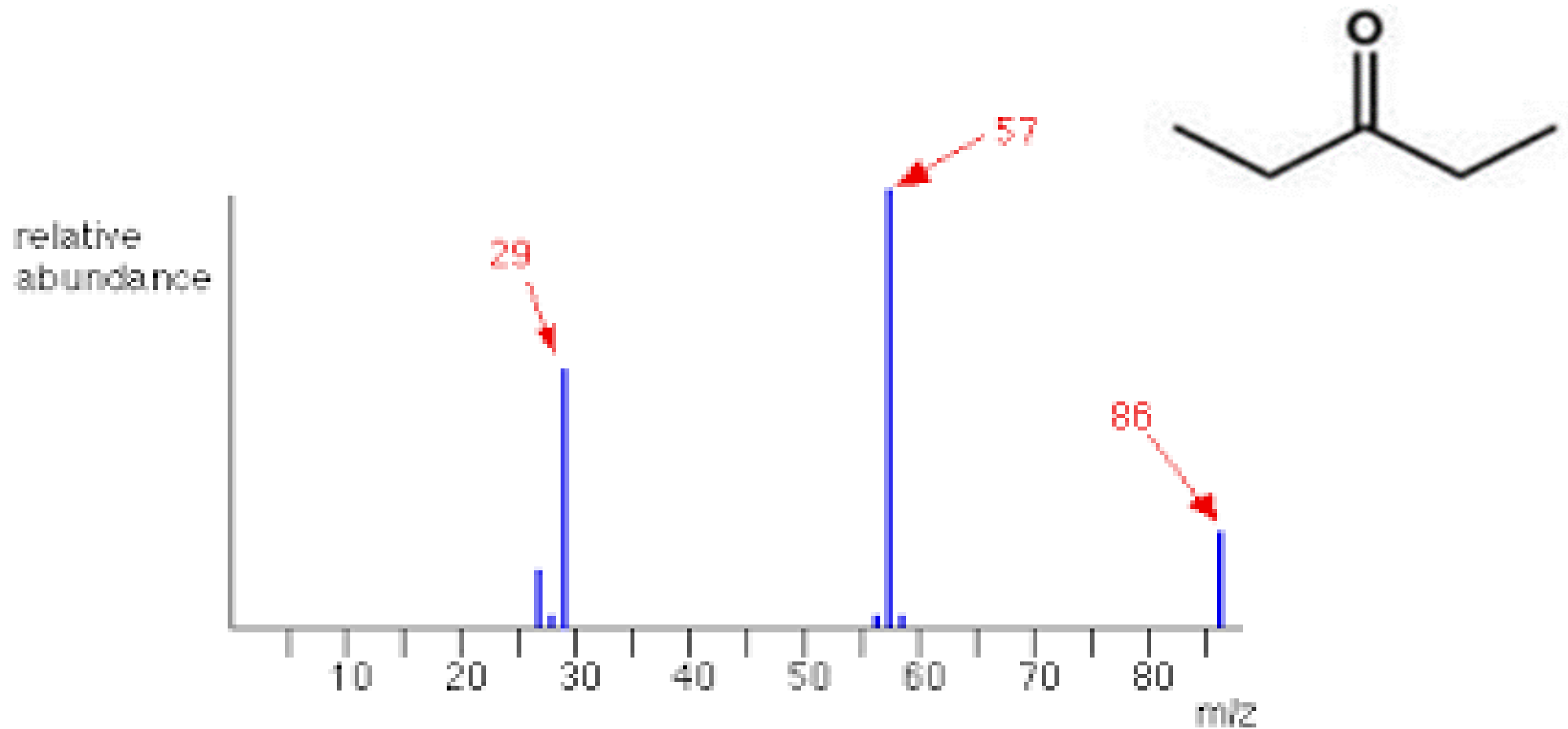
Ketones Fragmentation

- A common fragmentation pattern observed in ketones is the α cleavage occurring at the carbon–carbon bond at the α position next to the carbonyl group. The α cleavage generates a neutral alkyl radical and an acyl cation.
- Another characteristic fragmentation, is observed in long chain compounds with hydrogen at their γ carbon. The rearrangement forms a radical cation along with the loss of a neutral alkene. The alkene has an even mass, so the spectra often show a peak at $[M-x]$, where x is an even number.

- The mass spectrum of 2-pentanone (M.Wt. = 86). The base peak in this spectrum is again an acylium ion (43 m/z)



- The mass spectrum of 3-pentanone (M.Wt. = 86). The base peak in this spectrum is again an acylium ion (57 m/z)



- The mass spectrum of 2-hexanone (M.Wt. = 100) The base peak in this spectrum is again an acylium ion (43 m/z)

