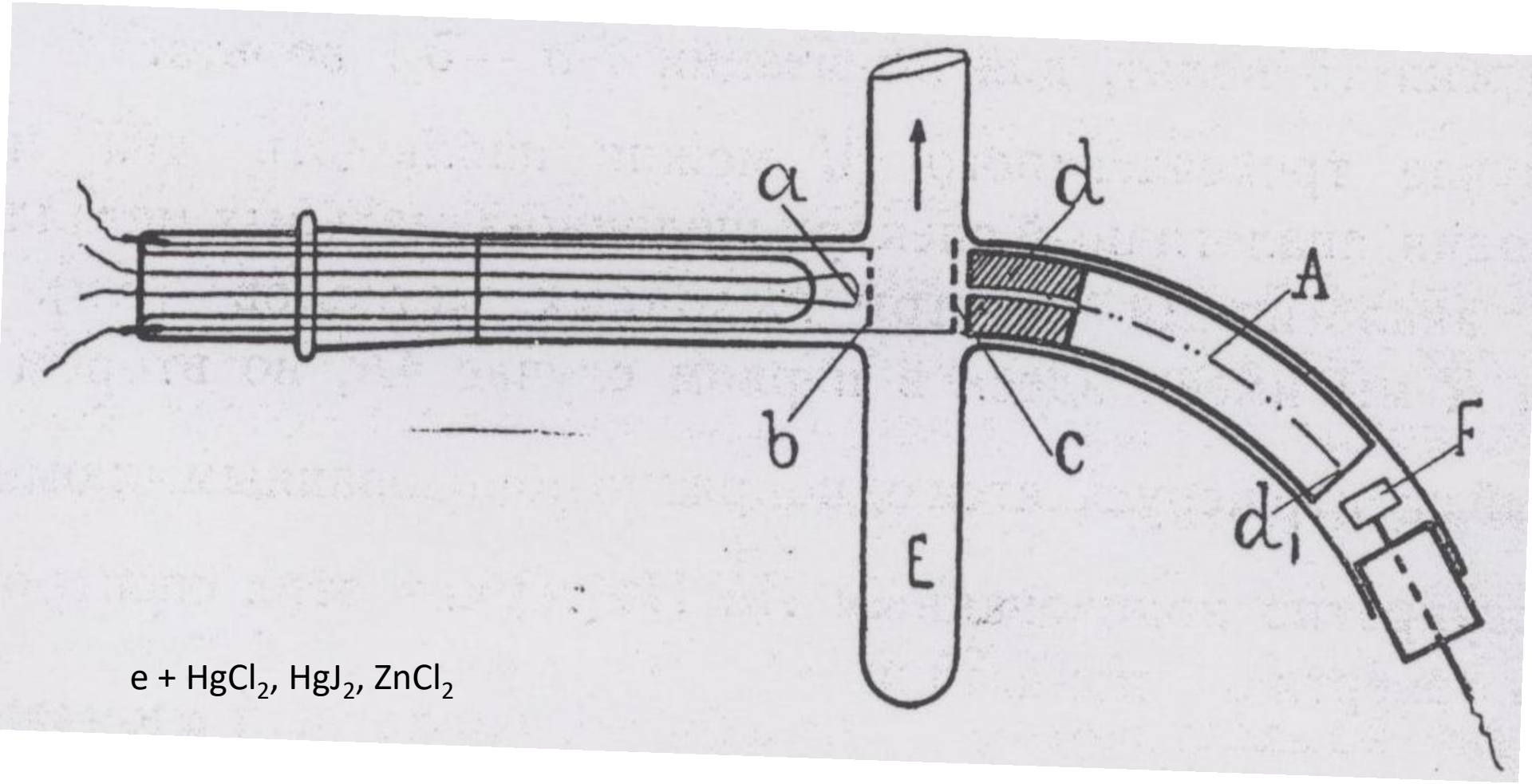
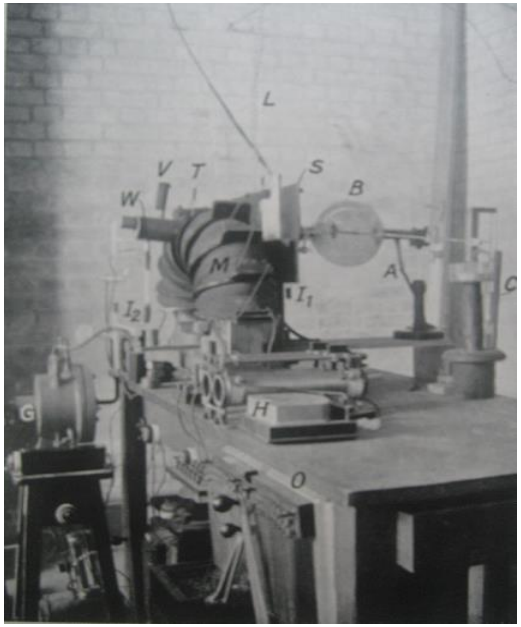
Ion molecular reactions: the beginning of research and recognition of chirality.

Evgeny Nikolaev
Skolkovo Institute of Science and Technology

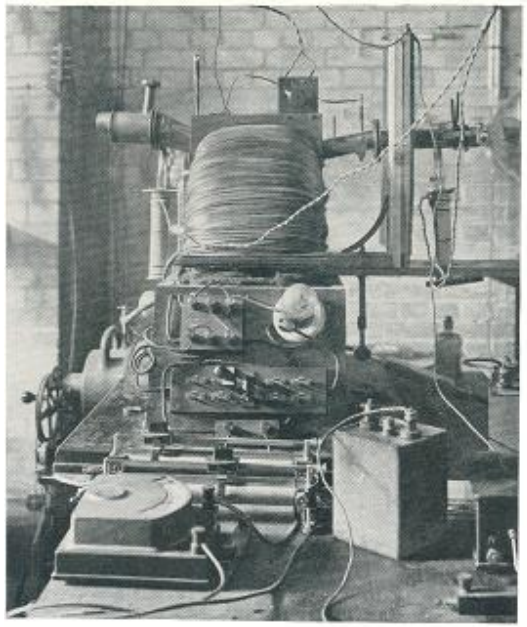
The first mass spectrometer in Soviet Union
N.N.Semenov and V.N.Kondratiev 1924



N.N.Semenov, Electron Phenomena (A.F. Ioffe editor)
Leningrad1928



1919



THE SECOND MASS-SPECTROGRAPH.

1925

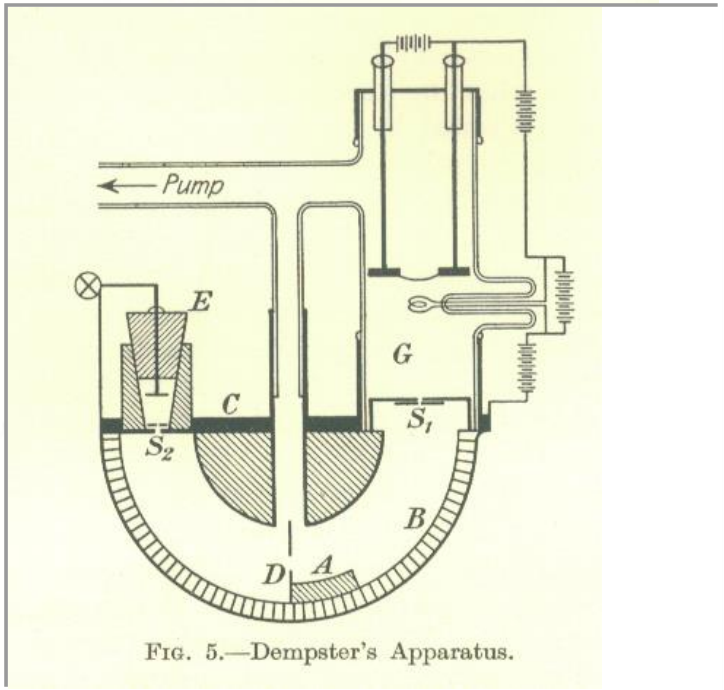
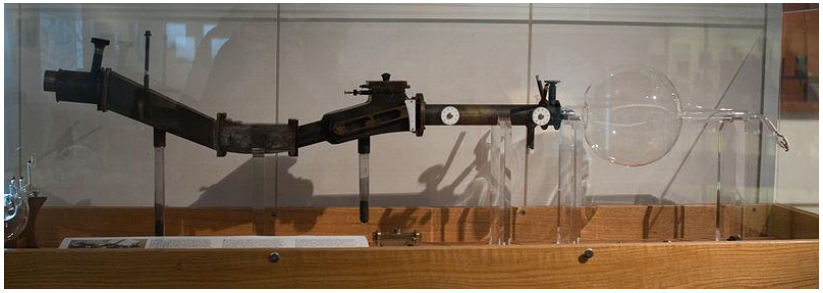


FIG. 5.—Dempster's Apparatus.

1918



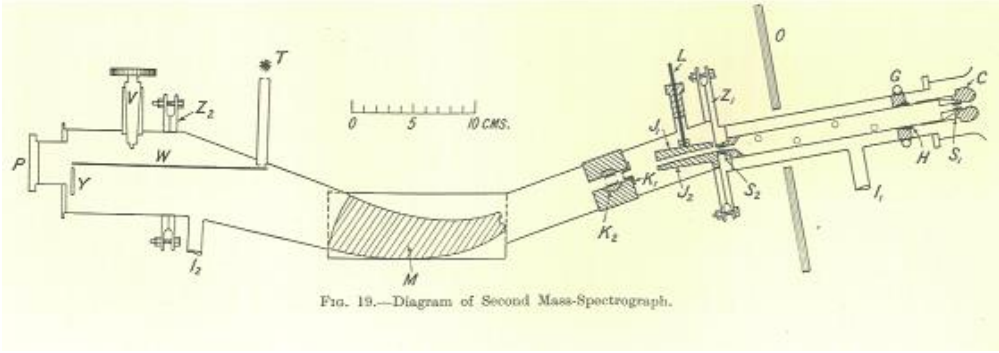
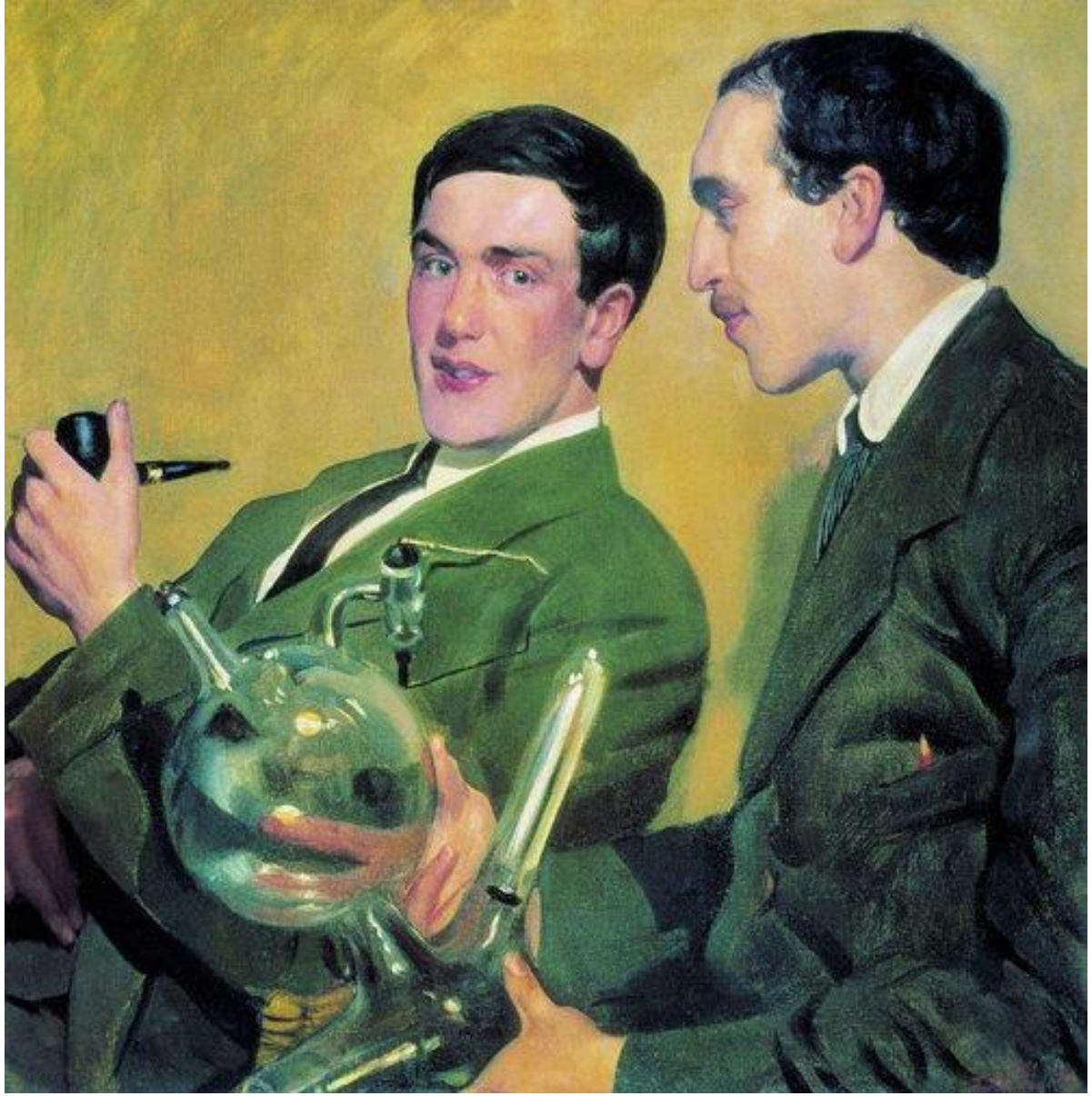


FIG. 19.—Diagram of Second Mass-Spectrograph.



Kustodiev B.M.

Portrait of Prof. Peter Kapitsa and Nikolay Semenov 1921

Edinburg 2003 г. Thomson medal laureates

JOURNAL OF MASS SPECTROMETRY

Special Feature: Historical

V. L. Tal'roze A. K. Ljubimova

Secondary processes in the ion source of a mass spectrometer (presented by academician N.N. Semenov 27 viii 1952)—reprinted from report of the Soviet Academy of Sciences, *Volume LXXXVI*, -n5 (1952)

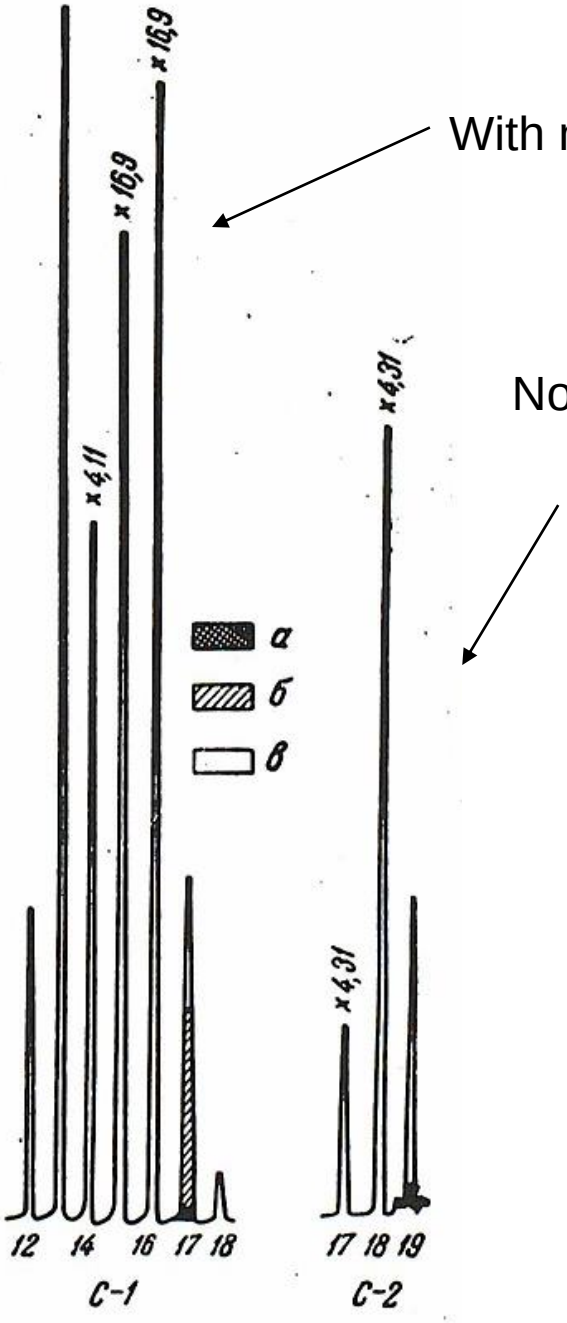
First published: 04 May 1999
https://doi.org/10.1002/(SICI)1096-9888(199806)33:6<502::AID-JMS685>3.0.CO;2-%23

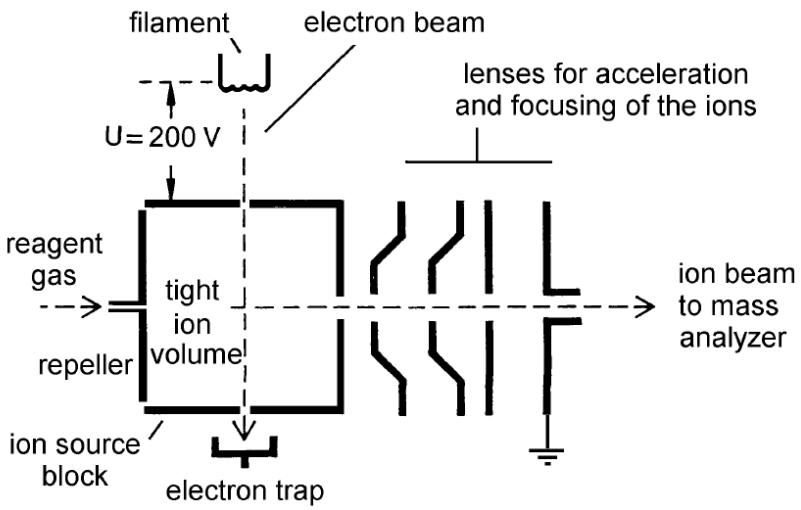

ATRIUM I & II

CH_5^+

With methane

No methane





Доклады Академии Наук СССР
1952. Том LXXXVI, № 5

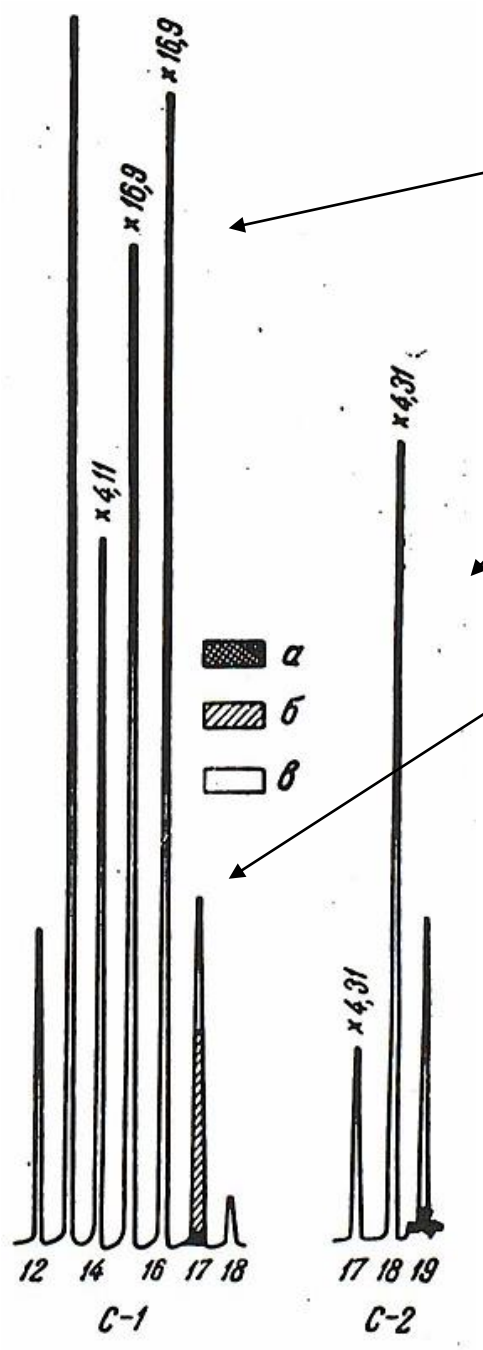
ФИЗИКА

В. Л. ТАЛЬРОЗЕ и А. К. ЛЮБИМОВА

ВТОРИЧНЫЕ ПРОЦЕССЫ В ИОННОМ ИСТОЧНИКЕ МАСС-СПЕКТРОМЕТРА

(Представлено академиком Н. Н. Семеновым 27 VIII 1952)

Нами исследованы вторичные процессы в газовом ионном источ-
масс-спектрометра в случаях, когда ионизации подвергаются
индивидуальные предельные (метан, этан, пропан, бутан) и непре-
пропилен, изобутилен) углеводороды, а также вода.



With methane

No methane

CH_5^+ (methonium)

$$CH_4 + e^- \rightarrow CH_4^{+\bullet}, CH_3^+, CH_2^{+\bullet}, CH^+, C^{+\bullet}, H_2^{+\bullet}, H^+$$

$$CH_4^{+\bullet} + CH_4 \rightarrow CH_5^+ + CH_3^\bullet$$

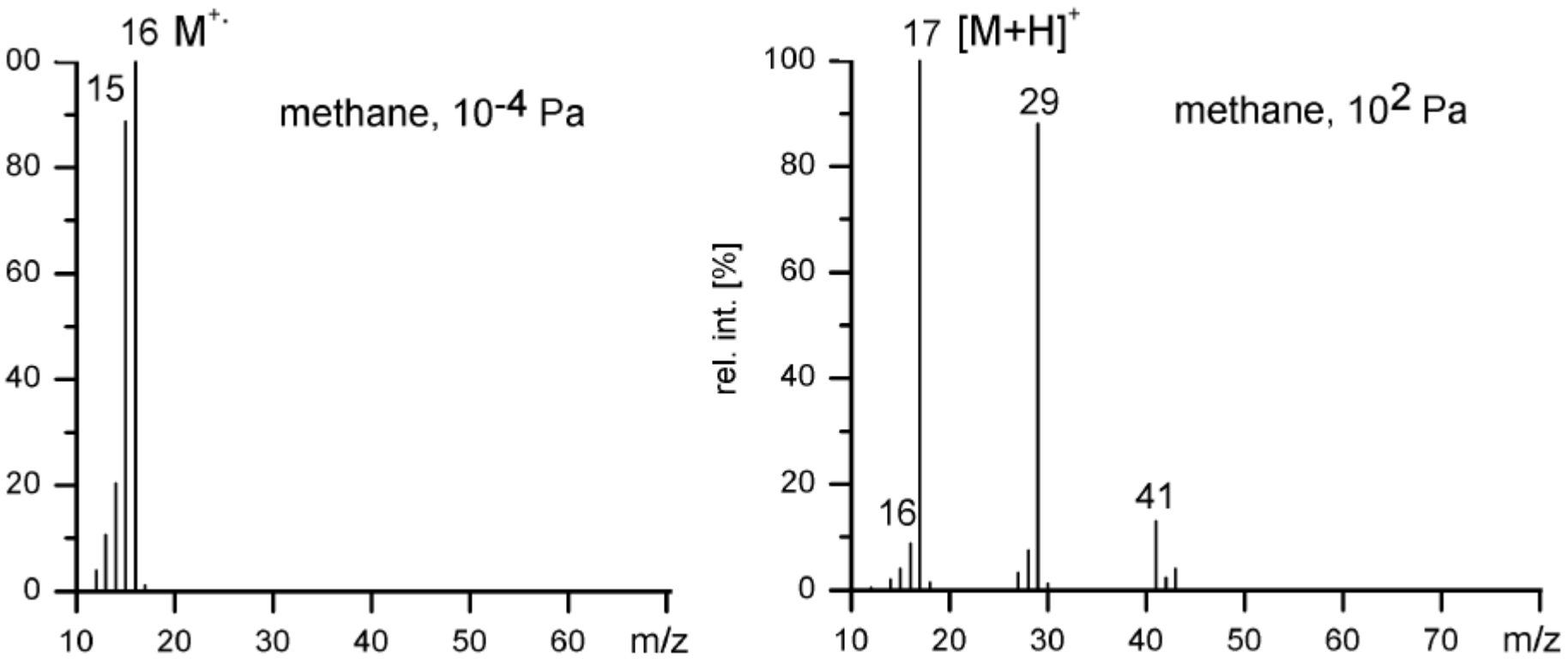
$$CH_3^+ + CH_4 \rightarrow C_2H_7^+ \rightarrow C_2H_5^+ + H_2$$

$$CH_2^{+\bullet} + CH_4 \rightarrow C_2H_4^{+\bullet} + H_2$$

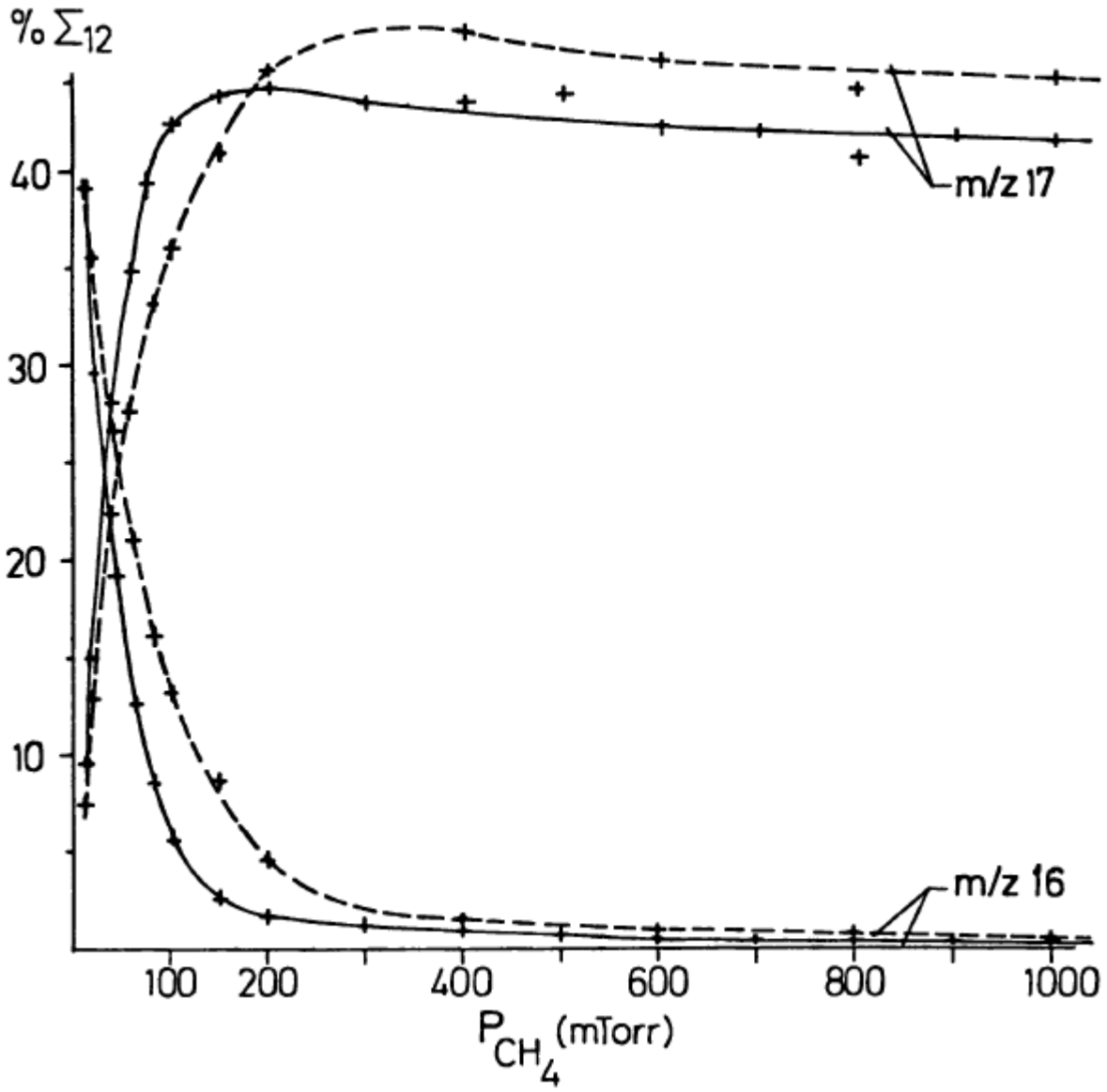
$$CH_2^{+\bullet} + CH_4 \rightarrow C_2H_3^+ + H_2 + H^\bullet$$

$$C_2H_3^+ + CH_4 \rightarrow C_3H_5^+ + H_2$$

$$C_2H_5^+ + CH_4 \rightarrow C_3H_7^+ + H_2$$



Comparison of the methane spectrum upon electron ionization at different ion source pressures: (**a**) approx. 10^{-4} Pa, (**b**) approx. 10^{2} Pa. The latter represents the typical methane reagent gas spectrum in positive-ion CI.



Percentage of total ionization above *m/z* 12 (% Σ12) of $CH^{4+\bullet}$, *m/z* 16, and CH^{5+}, *m/z* 17,

From Wikipedia

Methonium or CH_5^+ is protonated methane.

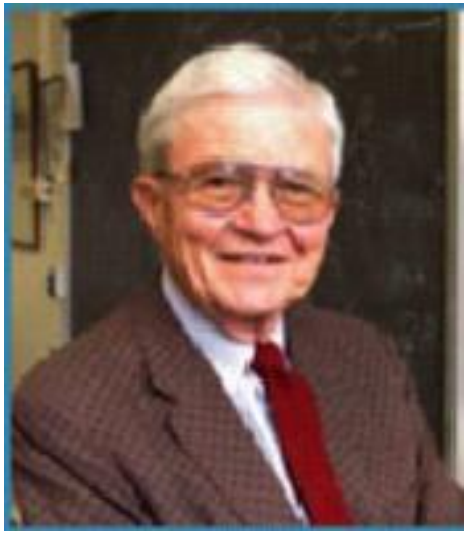
This ion exists as a reactive intermediate in interstellar space and can be produced in the laboratory in low concentrations in the gas phase at low temperatures.

This compound is considered a CH_3^+ carbenium ion with a molecule of hydrogen interacting with the empty orbital in a 3-center-2-electron bond.

CH_5^+

Mystery of the structure

Fred McLafferty



I do not believe….

The proof of CH5+ existence by resolving of m/z=17 multiplet.

Доклады Академии Наук СССР
1953. Том XCIII, № 6

ФИЗИКА

Н. Е. АЛЕКСЕЕВСКИЙ, В. Л. ТАЛЬРОЗЕ и В. Н. ШЕЛЯПИН

ДОКАЗАТЕЛЬСТВО СУЩЕСТВОВАНИЯ ИОНА CH_5^+ ПУТЕМ РАЗРЕШЕНИЯ МУЛЬТИПЛЕТА 17 В МАСС-СПЕКТРЕ МЕТАНА

(Представлено академиком Л. Д. Ландау 27 X 1953)

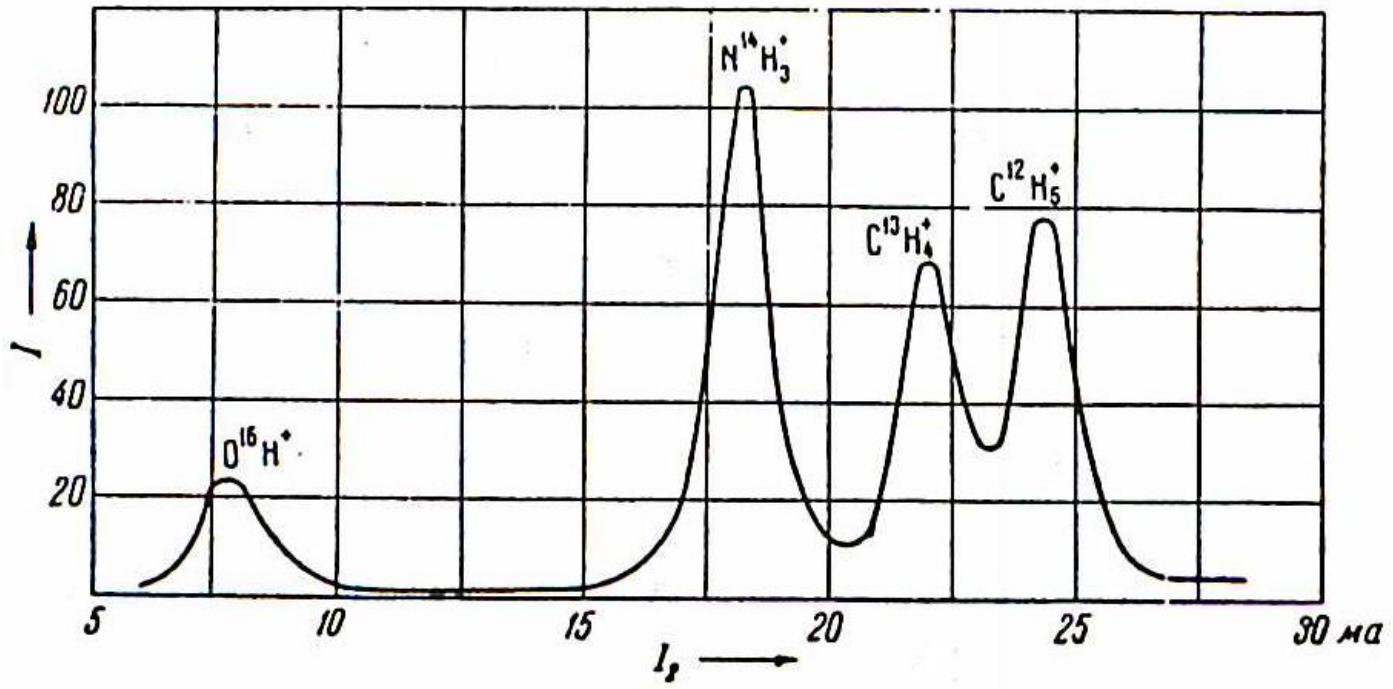


Рис. 1

Peter R. Schreiner,

Does CH_5^+ Have (a) Structure? A Tough Test for Experiment and Theory

Angewandte Chemie Volume 39, Issue 18 , Pages 3239 – 3241

Published Online: 13 Sep 2000

A. J. R. Heck, L. J. de Koning, N. M. M. Nibbering, *J. Am. Soc. Mass Spectrom.* **2**, 453 (1991).

… which showed that in the absence of intermolecular collisions, CH_4D^+ and CD_4H^+ are not rearranging but are stable. That these ions are relatively stable complexes of $[CH_3HD]^+$ and $[CD_3HD]^+$ was inferred from quenching reactions with NH_3

The two hydrogen atoms in H_2 can continuously exchange positions with the three hydrogen atoms in the CH_3^+ so the methonium ion is considered a FLUXIONAL molecule.

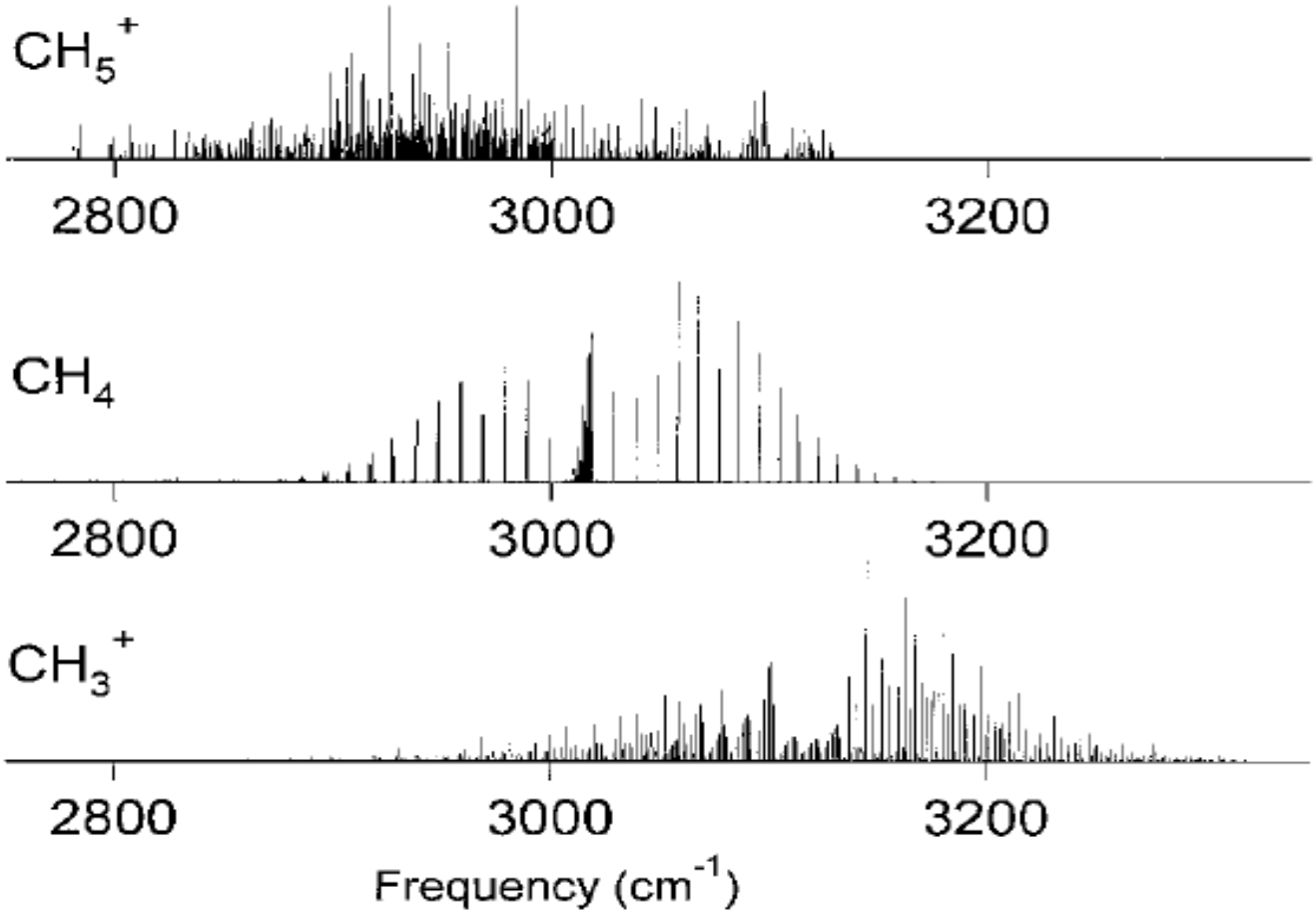
The energy barrier for the exchange is quite low and occurs even at very low temperatures.

Fluxional molecules are molecules which can undergo a "self" reaction wherein bonds rearrange to a structurally identical molecule. Isotopic labelling, however, can demonstrate that bonds have actually shifted

“In view of these arguments, it is likely that experiments performed systematically for a family of CH_5^+ isotopomers will lead to crucial novel insights into this fascinating molecular ion.

As we concluded in our perspective, CH_5^+ will certainly continue to challenge many groups in various fields of expertise for some time to come.”

SCIENCE VOL 286 5 NOVEMBER 1999 1051-1052a



Observed overall infrared spectrum of CH_5^+ as compared with spectra of CH_4^+ and CH_3^+

Understanding the Infrared Spectrum of Bare CH_5^+ Oskar Asvany, Padma Kumar P, Britta Redlich, Ilka Hegemann, Stephan Schlemmer, Dominik Marx , Science 309, 1219 (**2005**).

Quantum Deconstruction of the Infrared Spectrum of CH_5^+ Xinchuan Huang, Anne B. McCoy, Joel M. Bowman, Lindsay M. Johnson, Chandra Savage, Feng Dong, David J. Nesbitt Science 311, 60 - 63 (**2006)**

Chemical ionization

In a CI experiment, ions are produced through the collision of the analyte with ions of a reagent gas that are present in the ion source. Some common reagent gases include: methane, ammonia, and isobutane. Inside the ion source, the reagent gas is present in large excess compared to the analyte. Electrons entering the source will preferentially ionize the reagent gas. The resultant collisions with other reagent gas molecules will create an ionization plasma. Positive and negative ions of the analyte are formed by reactions with this plasma.

Primary ion formation

$$CH_4 + e^- \longrightarrow CH_4^{+\bullet} + 2\,e^-$$

Secondary reagent ions

$$CH_4 + CH_4^{+\bullet} \longrightarrow CH_5^+ + CH_3^\bullet$$

$$CH_4 + CH_3^+ \longrightarrow C_2H_5^+ + H_2$$

Product ion formation

$$M + CH_5^+ \longrightarrow CH_4 + [M+H]^+ \quad \text{(protonation)}$$

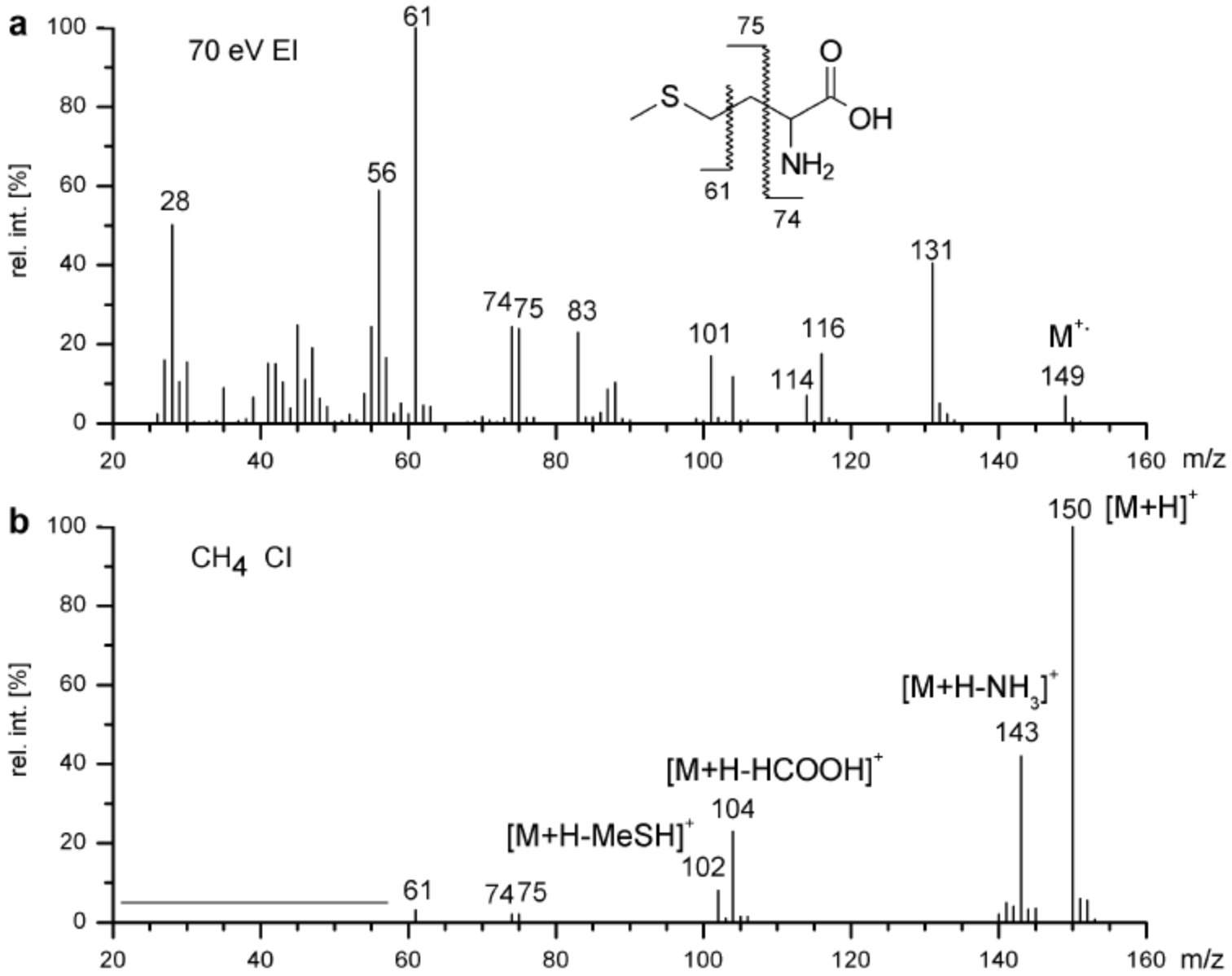
$$AH + CH_3^+ \longrightarrow CH_4 + A^+ \quad (H^- \text{ abstraction})$$

$$M + C_2H_5^+ \longrightarrow [M + C_2H_5]^+ \quad \text{(adduct formation)}$$

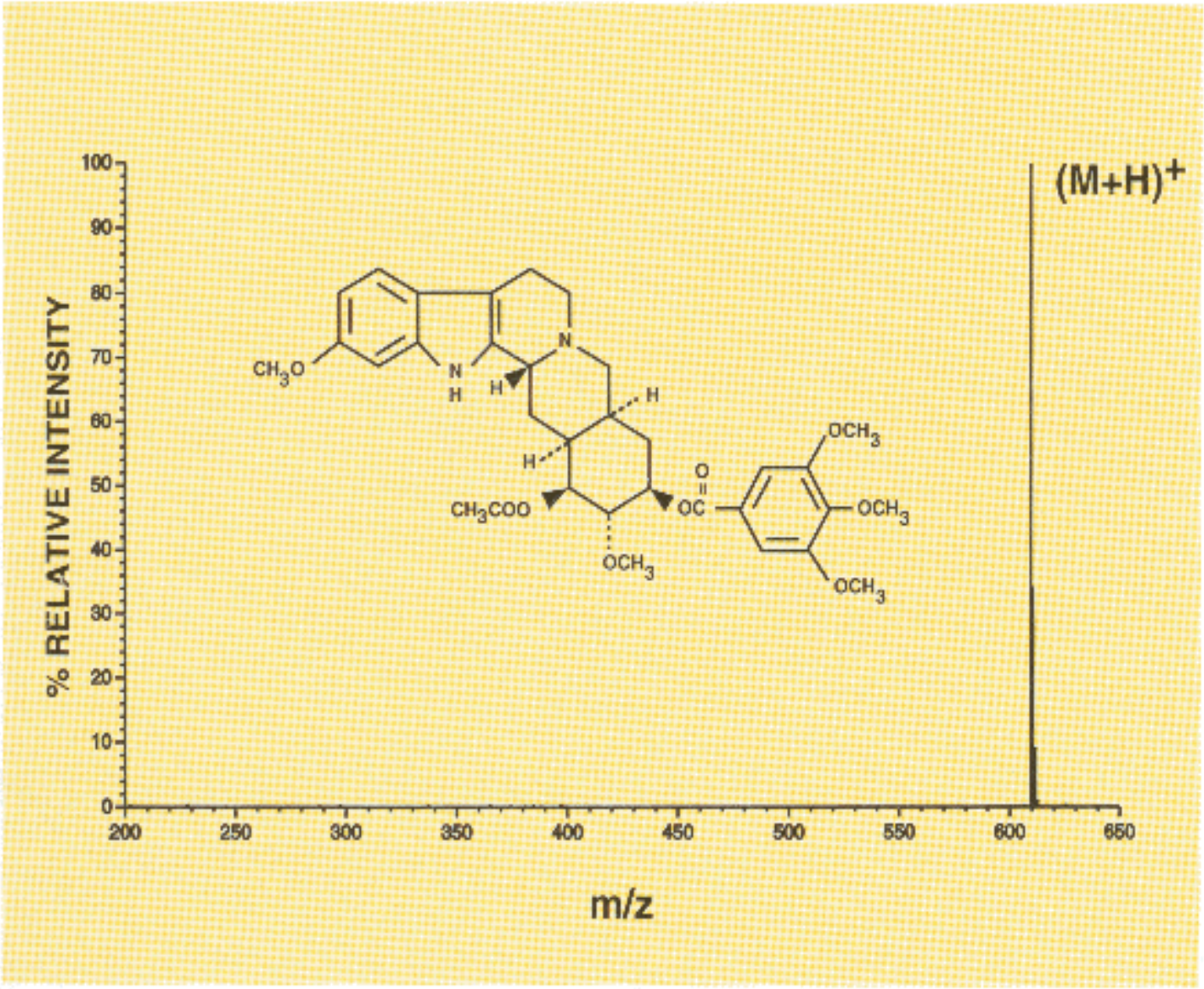
$$A + CH_4^+ \longrightarrow CH_4 + A^+ \quad \text{(charge exchange)}$$

Self chemical ionization occurs when the reagent ion is an ionized form of the analyte.

Munson, M.S.B.; Field, F.H. *J. Am. Chem. Soc.* **1966**, *88*, 2621-2630. Chemical Ionization Mass Spectrometry. I. General Introduction



Comparison of (**a**) 70 eV EI spectrum and (**b**) methane reagent gas CI spectrum of the amino acid methionine. Fragmentation is strongly reduced in the CI mass spectrum.



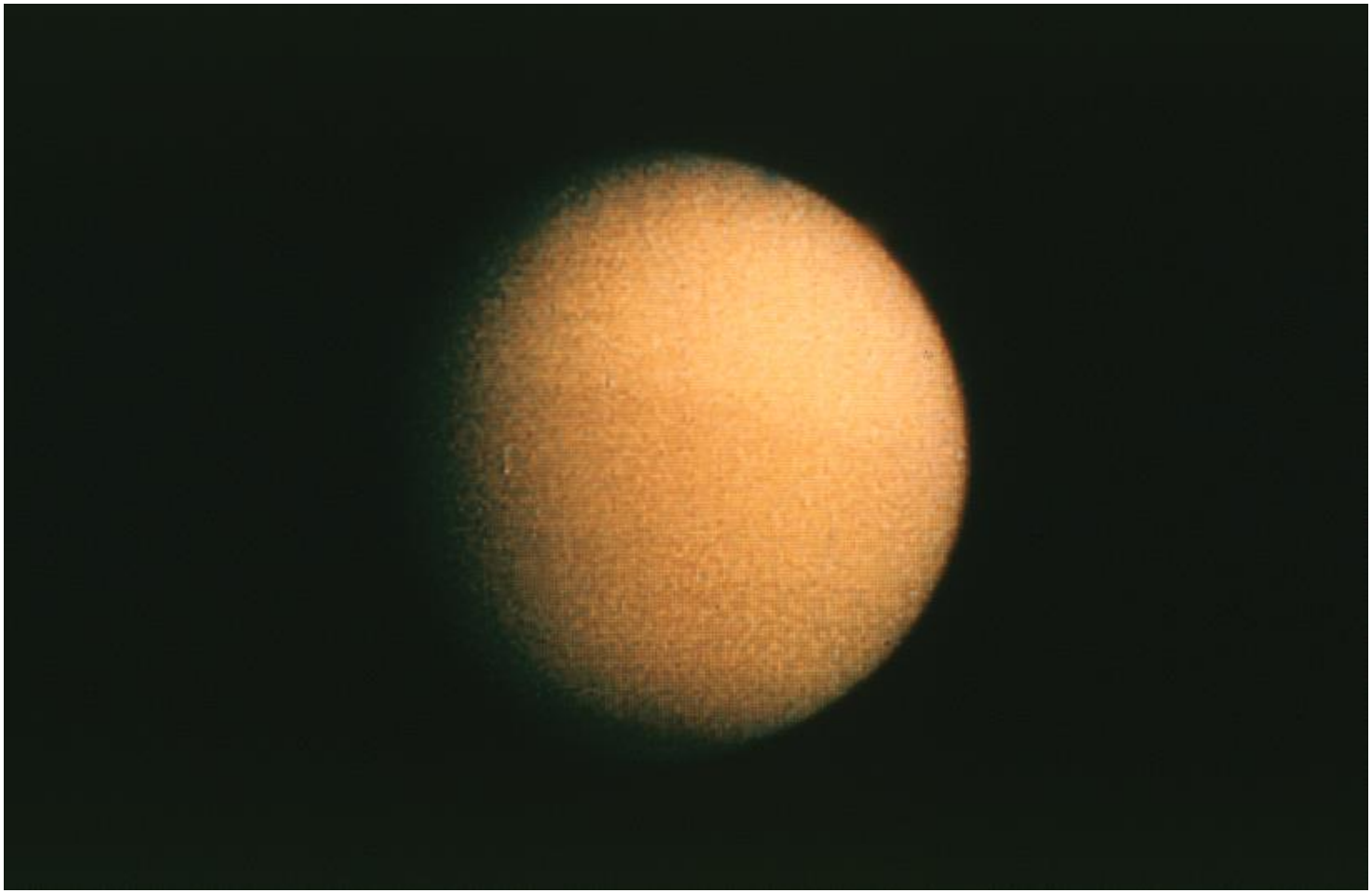
APCI mass spectrum of reserpine taken during an LC/MS run.

Vaporization Assembly

Corona Needle

Surprising application

Titan

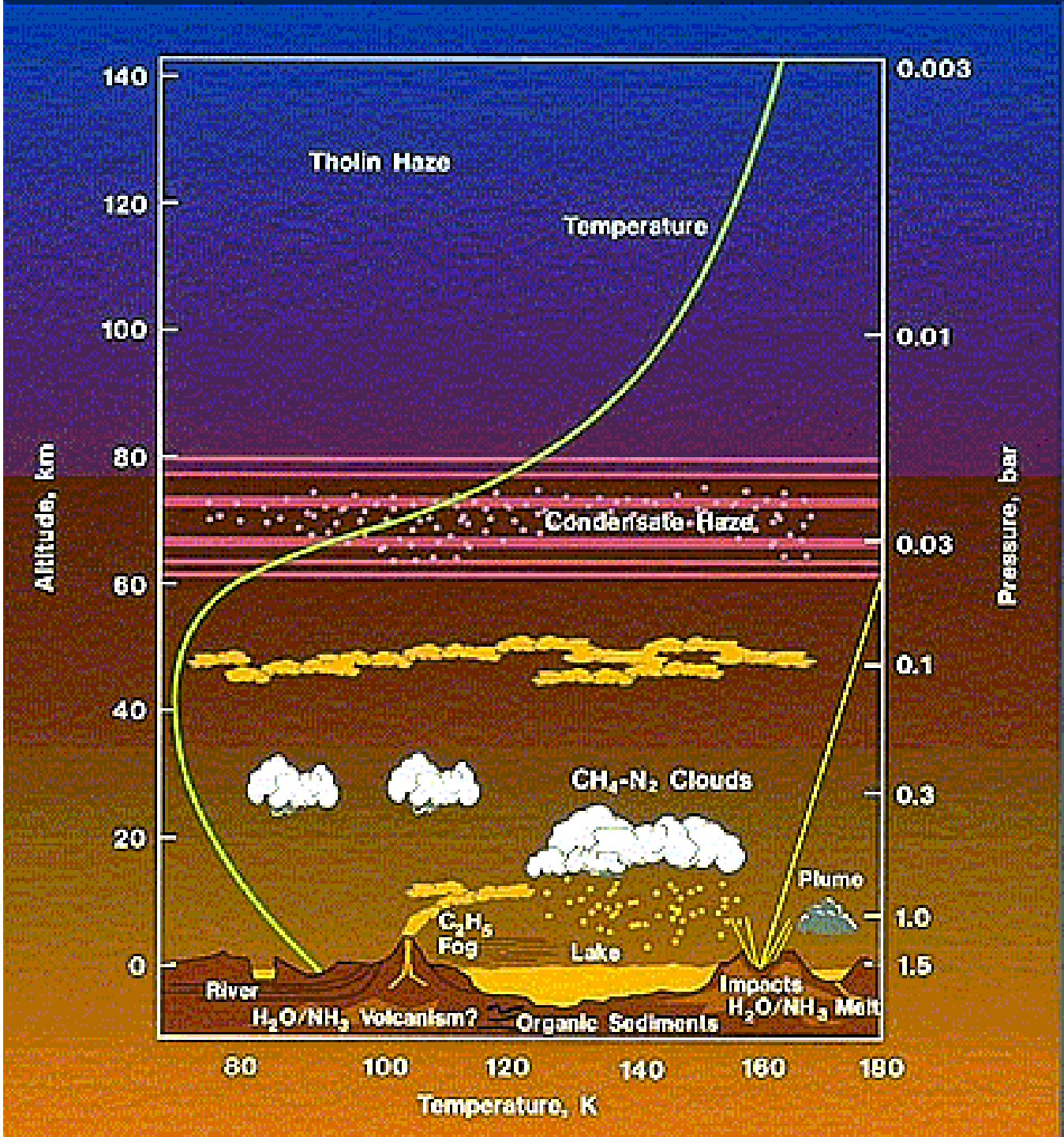


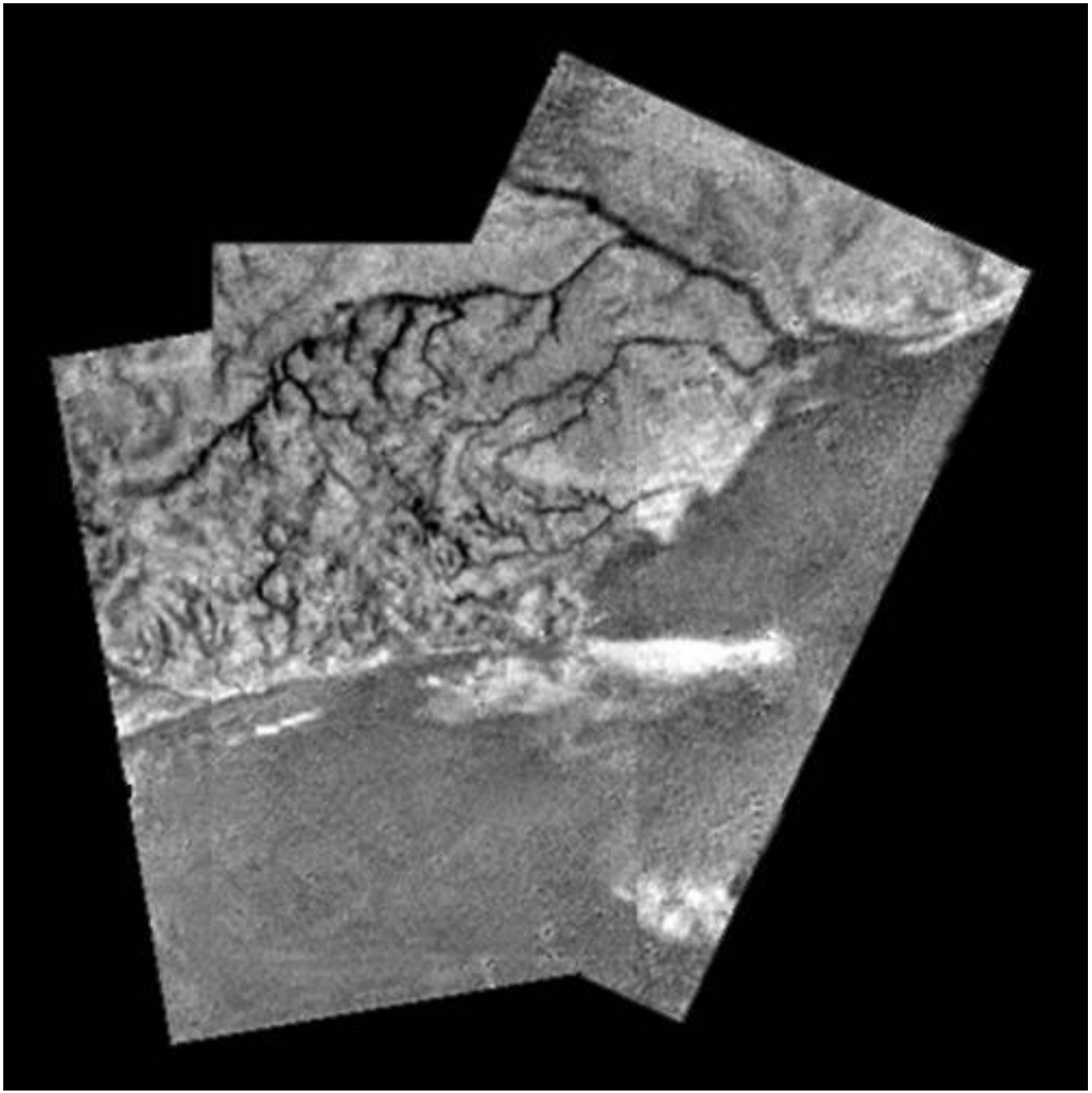
Titan surface and atmosphere:

T(surface) 95 K;

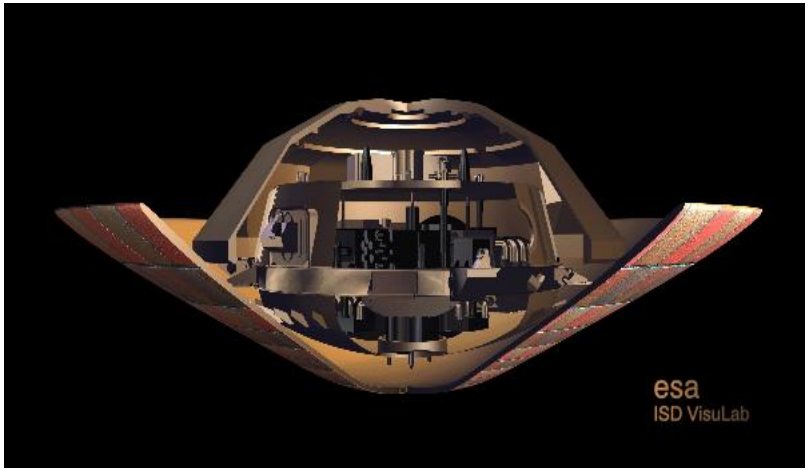
$P(N_2)$=1.5 bar.;
CH_4 2-10%;

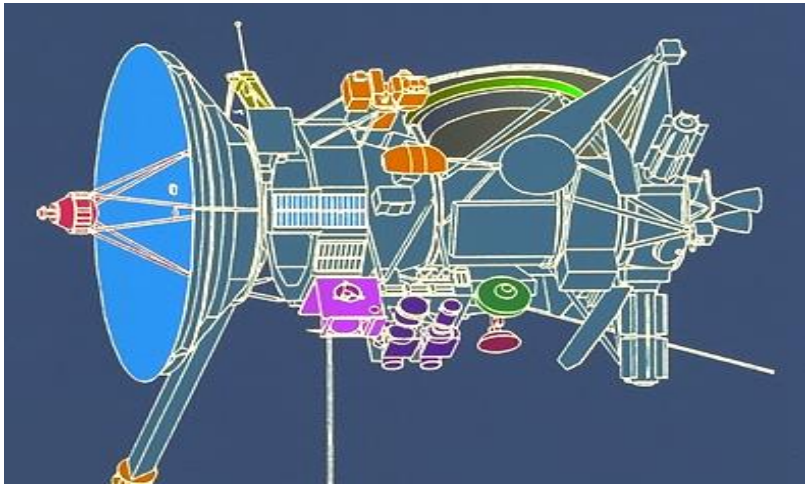
Organic deposits on the surface~1 км, liquids of hydrocarbon



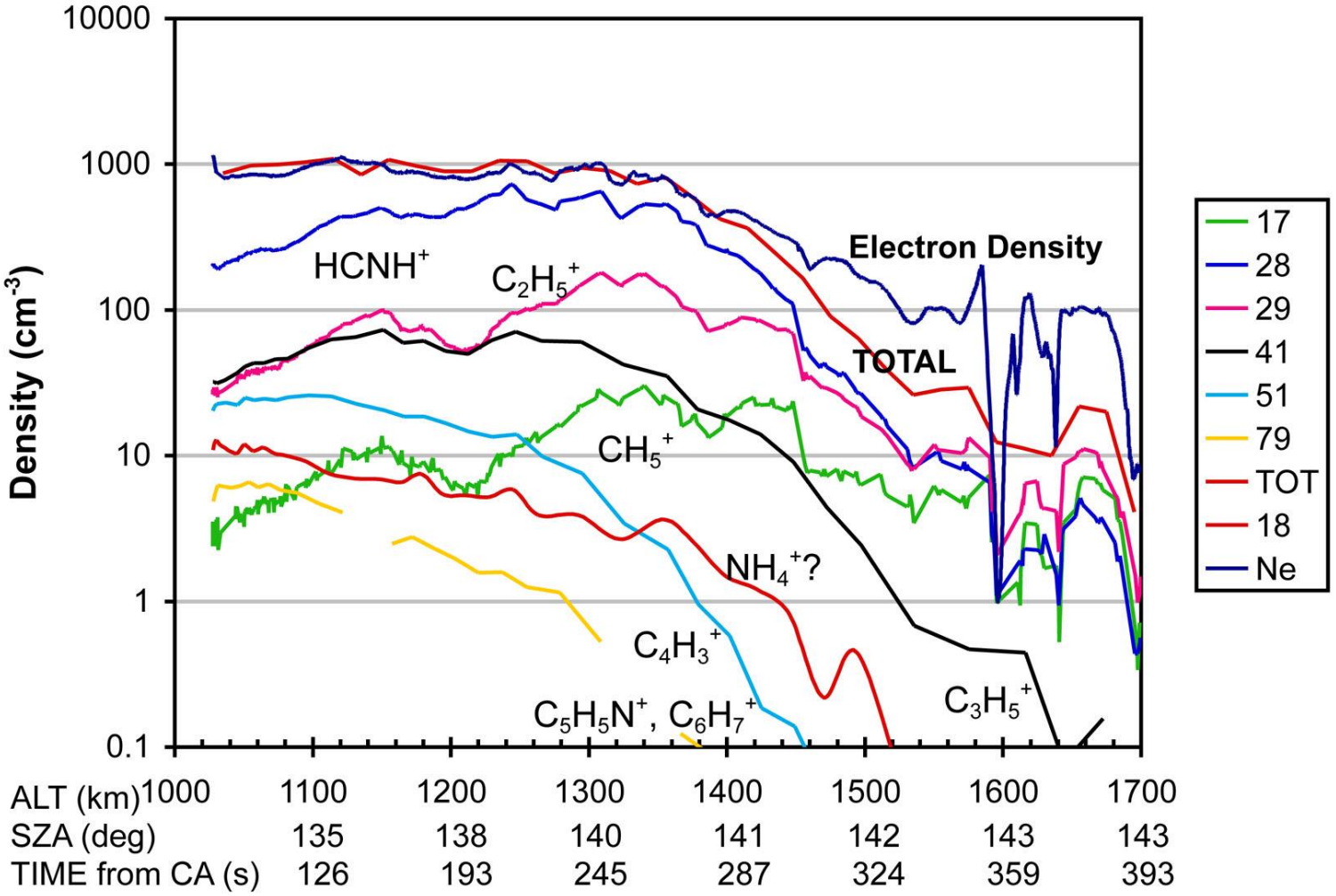


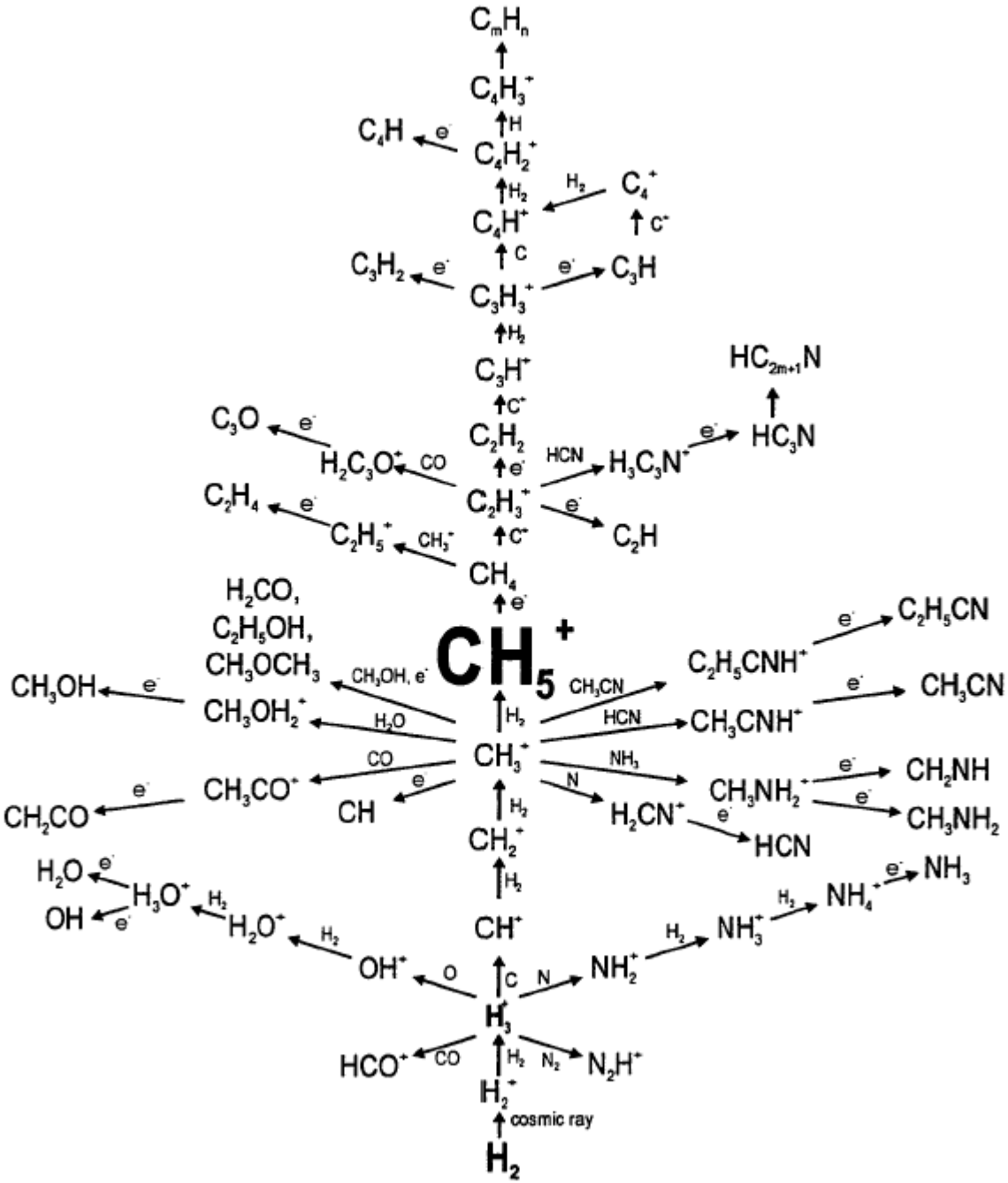
Cassini–Huygens mission to Titan





Density profiles of several important ion species. Densities measured by the INMS are shown versus altitude, time from CA, and solar zenith angle (SZA) for the outbound T5 encounter of Cassini with Titan. The latitude and local solar time at CA are 73.7 deg. N and 0.7 hrs., respectively. Total INMS ion density and an electron density profile measured by the RPWS experiment are also shown.




C_mH_n
$C_4H_3^+$
H
C_4H
e⁻
$C_4H_2^+$
H_2
C_4^+
C_4H^+
C⁻
C
C_3H_2
e⁻
e⁻
C_3H
$C_3H_3^+$
H_2
C_3H^+
$HC_{2m+1}N$
C⁺
C_3O
e⁻
C_2H_2
HC_3N
$H_2C_3O^+$
CO
e⁻
HCN
$H_3C_3N^+$
C_2H_4
e⁻
$C_2H_3^+$
e⁻
C_2H
$C_2H_5^+$
CH_3^-
C⁻
CH_4
e⁻
H_2CO,
C_2H_5OH,
CH_3OCH_3
CH_5^+
C_2H_5CN
e⁻
$C_2H_5CNH^+$
CH_3OH
e⁻
CH_3OH, e⁻
CH_3CN
CH_3CN
e⁻
$CH_3OH_2^+$
H_2O
H_2
HCN
CH_3CNH^+
CO
NH_3
CH_2NH
e⁻
$CH_3NH_2^+$
e⁻
CH_3CO^+
e⁻
N
CH_3NH_2
CH_2CO
e⁻
CH
CH_3^+
H_2CN^+
e⁻
HCN
H_2
CH_2^+
H_2
H_2O
e⁻
H_3O^+
H_2
NH_4^+
e⁻
NH_3
H_2
OH
e⁻
H_2O^+
H_2
CH⁺
H_2
NH_3^+
OH^+
O
C
N
NH_2^+
H_3^+
HCO^+
CO
H_2
N_2
N_2H^+
H_2^+
cosmic ray
H_2

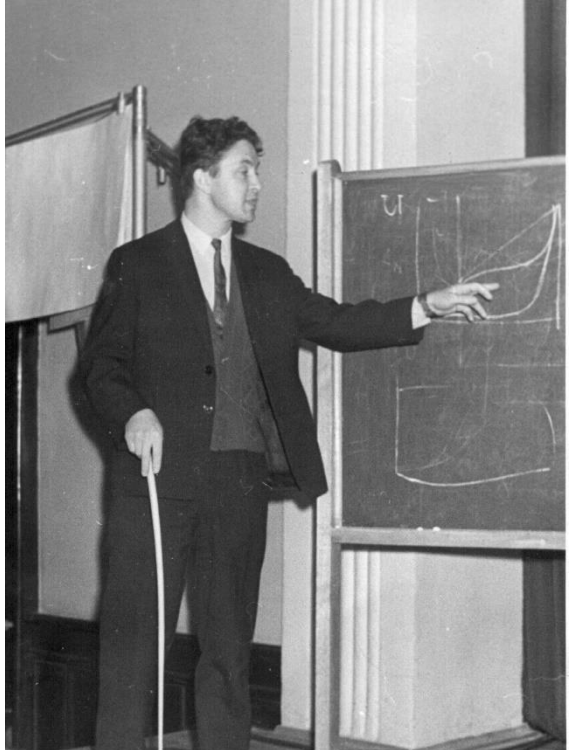
JACS **80**,9(1958) 2344

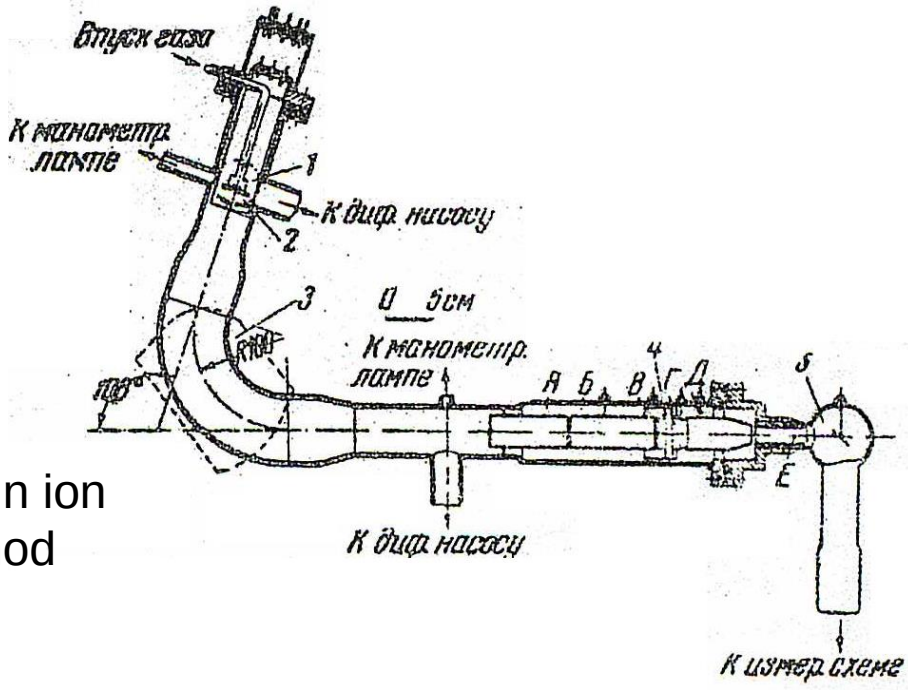
DETERMINATION OF PROTON AFFINITY AND BOND DISSOCIATION ENERGY BY ION IMPACT METHOD

Sir:

Until recently there were no experimental methods for the determination of the proton affinity of saturated molecules. A method for such a determination has been proposed by the authors[1] and it consists in investigating reactions between ions and molecules in the ionization chamber of a mass spectrometer. If, under the experimental conditions, a reaction can be observed, one may conclude that the reaction has no activation energy (to within an accuracy of 1–2 kcal./mole) and that it is either thermoneutral or exothermic. If a reaction is not observed one may conclude that it is endothermic. After a number of reactions have been investigated, the above criterion can be used to set up a series of inequalities and to determine thereby the limits within which either the proton

(1) V. L. Tal'rose and E. L. Frankevitch, *Doklady Akad. Nauk S.S.S.R.*, **111**, No. 2, 37 (1956).





Evgeny Frankevich
Discovering of absence of activation energies in ion molecular reactions and fork (bracketing) method

Пусть R_1H и R_2H — водородсодержащие молекулы: R_1 и R_2 — любые радикалы; M — молекула, сродство к протону которой мы хотим определить.

Предположим, что процесс

А. $R_1H + M^+ = R_1 + MH^+$ обнаруживается,

а процесс

Б. $R_2H + M^+ = R_2 + MH^+$ не обнаруживается.

Observed
Not observed

Тогда можно утверждать, что

$$D(R_1 - H) + I(H) - I(M) < P_M < D(R_2 - H) + I(H) - I(M), \quad (а)$$

где $D(R—H)$ — энергия диссоциации связи R—H; $I(M)$ — потенциал ионизации частицы M; P_M — сродство к протону частицы M.

Другой случай: процесс

В. $R_1H^+ + M = R_1 + MH^+$ обнаруживается,

а процесс

Г. $R_2H^+ + M = R_2 + MH^+$ не обнаруживается.

Observed
Not observed

Тогда

$$D(R_1 - H) + I(H) - I(R_1H) < P_M < D(R_2 - H) + I(H) - I(R_2H). \quad (б)$$

fork (bracketing) method

Таким образом, величина P_M берется в «вилку». Естественно, что, стремясь получить наиболее узкую «вилку», можно комбинировать попарно любые из процессов А, Б, В и Г. Подбирая наиболее подходящие R_1H и R_2H, можно, повидимому, в ряде случаев сделать эту «вилку» достаточно узкой и оценить величину P_M с довольно большой точностью.

Table I

Upper and lower limits, kcal./mole	Reactions by which upper and lower limits were obtained	Mean values, kcal./mole	Data obtained by the electron impact method
171	$H_2O + C_2H_2^+ \not\rightarrow H_2O^+ + C_2H_2$	169[1]	...
167	$H_2O + H_2S^+ \rightarrow H_2O^+ + HS$		
183	$CH_3OH + NH_3^+ \not\rightarrow CH_3OH_2^+ + NH_3$	180	...
177	$CH_3OH^+ + H_2O \rightarrow CH_3OH_2^+ + OH$		
202	$C_2H_5OH + C_6H_6^+ \not\rightarrow C_2H_5OH_2^+ + C_6H_6$	193	...
185	$C_2H_5OH^+ + H_2O \rightarrow C_2H_5OH_2^+ + OH$		
79	$H_2^+ + C_2H_2 \not\rightarrow H_3^+ + C_2H$	70	...
61	$H_2^+ + H_2 \rightarrow H_3^+ + H$		
129	$CH_4^+ + H_2O \not\rightarrow CH_5^+ + OH$	122	...
114	$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$		

Пусть R_1H и R_2H — водородсодержащие молекулы: R_1 и R_2 — любые радикалы; M — молекула, сродство к протону которой мы хотим определить.

Предположим, что процесс

А. $R_1H + M^+ = R_1 + MH^+$ обнаруживается,

а процесс

Б. $R_2H + M^+ = R_2 + MH^+$ не обнаруживается.

Тогда можно утверждать, что

$$D(R_1 - H) + I(H) - I(M) < P_M < D(R_2 - H) + I(H) - I(M), \qquad (а)$$

где $D(R—H)$ — энергия диссоциации связи R—H; $I(M)$ — потенциал ионизации частицы M; P_M — сродство к протону частицы M.

Другой случай: процесс

В. $R_1H^+ + M = R_1 + MH^+$ обнаруживается,

а процесс

Г. $R_2H^+ + M = R_2 + MH^+$ не обнаруживается.

Тогда

$$D(R_1 - H) + I(H) - I(R_1H) < P_M < D(R_2 - H) + I(H) - I(R_2H). \qquad (б)$$

Таким образом, величина P_M берется в «вилку». Естественно, что, стремясь получить наиболее узкую «вилку», можно комбинировать попарно любые из процессов А, Б, В и Г. Подбирая наиболее подходящие R_1H и R_2H, можно, повидимому, в ряде случаев сделать эту «вилку» достаточно узкой и оценить величину P_M с довольно большой точностью.

Метод «вилки»

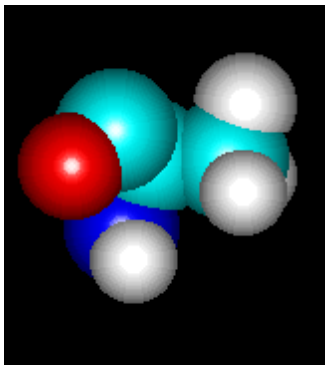
Now 166.7 kcal/mole

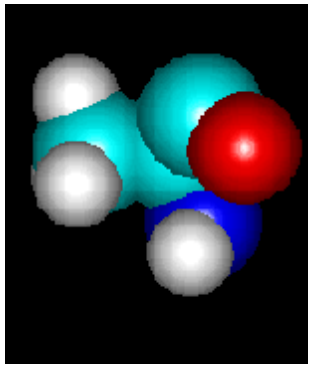
Table I

Upper and lower limits, kcal./mole	Reactions by which upper and lower limits were obtained	Mean values, kcal./mole	Data obtained by the electron impact method
171	$H_2O + C_2H_2^+ \not\rightarrow H_2O^+ + C_2H_2$	169[1]	...
167	$H_2O + H_2S^+ \rightarrow H_2O^+ + HS$		
183	$CH_3OH + NH_3^+ \not\rightarrow CH_3OH_2^+ + NH_2$	180	...
177	$CH_3OH^+ + H_2O \rightarrow CH_3OH_2^+ + OH$		
202	$C_2H_5OH + C_6H_6^+ \not\rightarrow C_2H_5OH_2^+ + C_6H_5$	193	...
185	$C_2H_5OH^+ + H_2O \rightarrow C_2H_5OH_2^+ + OH$		
79	$H_2^+ + C_2H_2 \not\rightarrow H_3^+ + C_2H$	70	...
61	$H_2^+ + H_2 \rightarrow H_3^+ + H$		
129	$CH_4^+ + H_2O \not\rightarrow CH_5^+ + OH$	122	...
114	$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$		

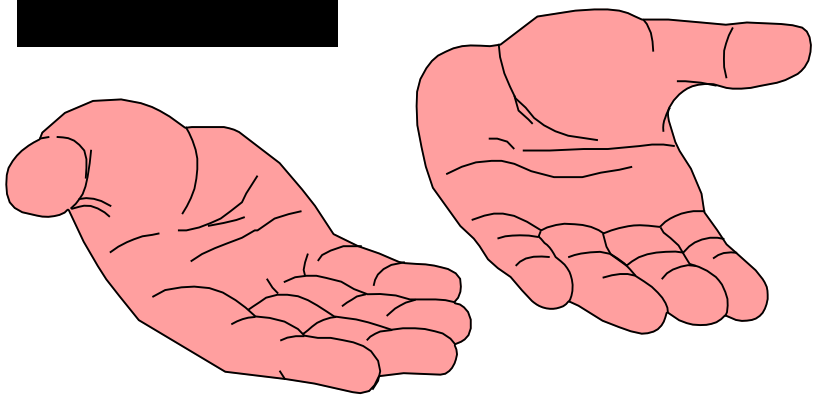
Chirality

L-alanine



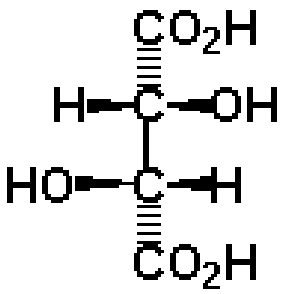


D-alanine

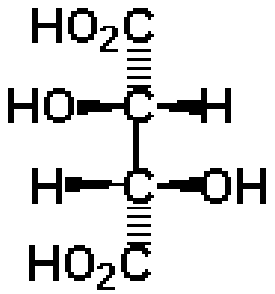


Homochirogenesis

Chirality discovered by L. Pasteur on 19th century



D-Tartaric Acid



L-Tartaric Acid

Pasteur, M. L. Ann. Chim. Phys. 1848, 24, 442.

Motivations for research in this field

- Asymmetry in biological systems (left amino acids / right sugars).
- Origin of chiral asymmetry - origin of life
- Basis of chirality conservation is chiral recognition via supramolecular interactions.
- Enantiomers differ in potency, pharmacological action, metabolism.

Symmetry Breaking

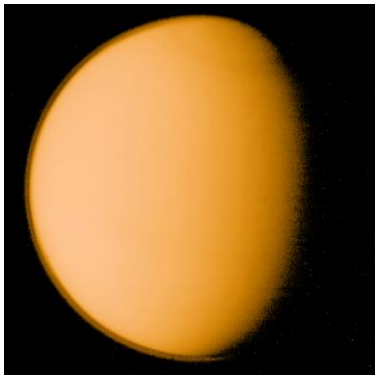
Symmetry breaking consists in the discrimination against one of the enantiomeric forms by a physical, chemical or statistical process.

How did it occur?

-External chiral agents

-Biochemical evolution

Generation of chirality on Titan



- Plenty of energy sources (UV, cosmic rays,…)
- Aerosol particles are irregularly-shaped, may polarize light under certain conditions
- Infall of meteorites, especially early on, may have brought in non-racemic mixture of amino acids
- Large spatial and temporal scales on the surface might encourage amplification of asymmetry
- Unique opportunity to test for generation of chirality in planetary-scale, abiotic organic system

The abiotic generation of homochirality on Saturn's moon Titan. Lunine, J. I.; Beauchamp, J.; Smith, M. A.; Nikolaev, E.. Advances in Biochirality (1999), 257-270.

What is a mechanism of molecular recognition of chirality?
How can mass spectrometry address this questions?
Mass spectrometry the most sensitive but intrinsically achiral!

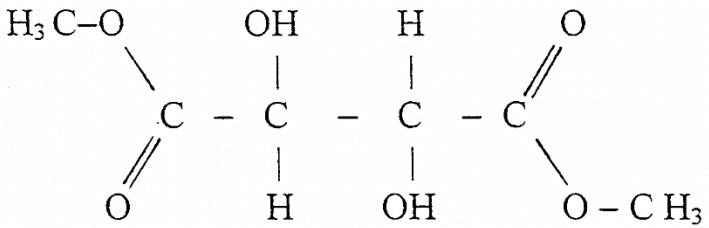
How can it help?

Methods of investigation of chirality effects in ion-molecule interactions

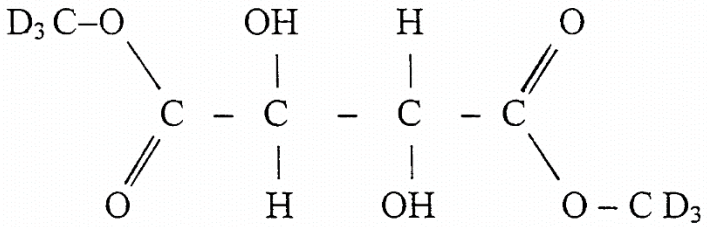
- Chiral ion -chiral molecule equilibrium investigation
- Measurement of the supramolecular complex decomposition rate constant dependence on chirality
- Measurement of complex formation rate constant dependence on chirality

Dimethyltartrate-classical object for investigations of chirality effects. It is similar to tartaric acid and salt but more volatile (10^{-6} Torr saturated pressure)

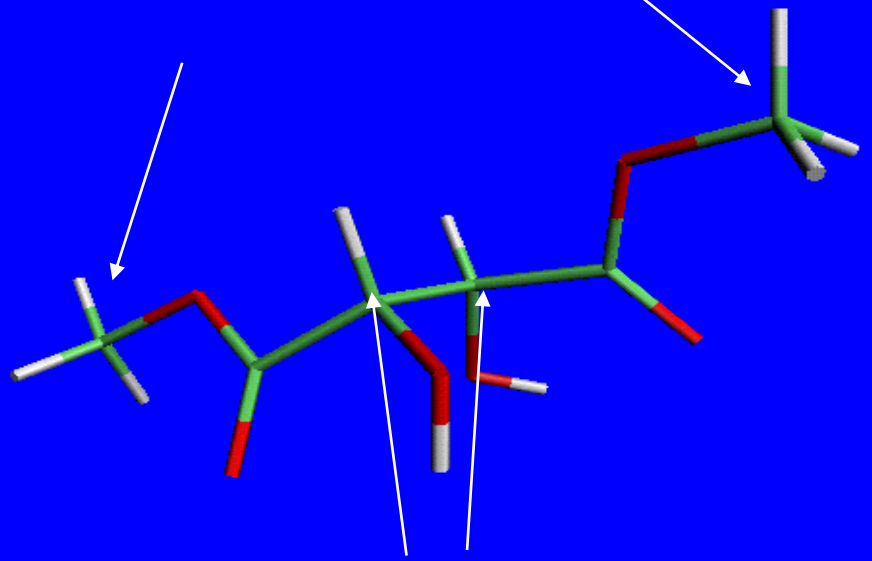
L,D-DMT



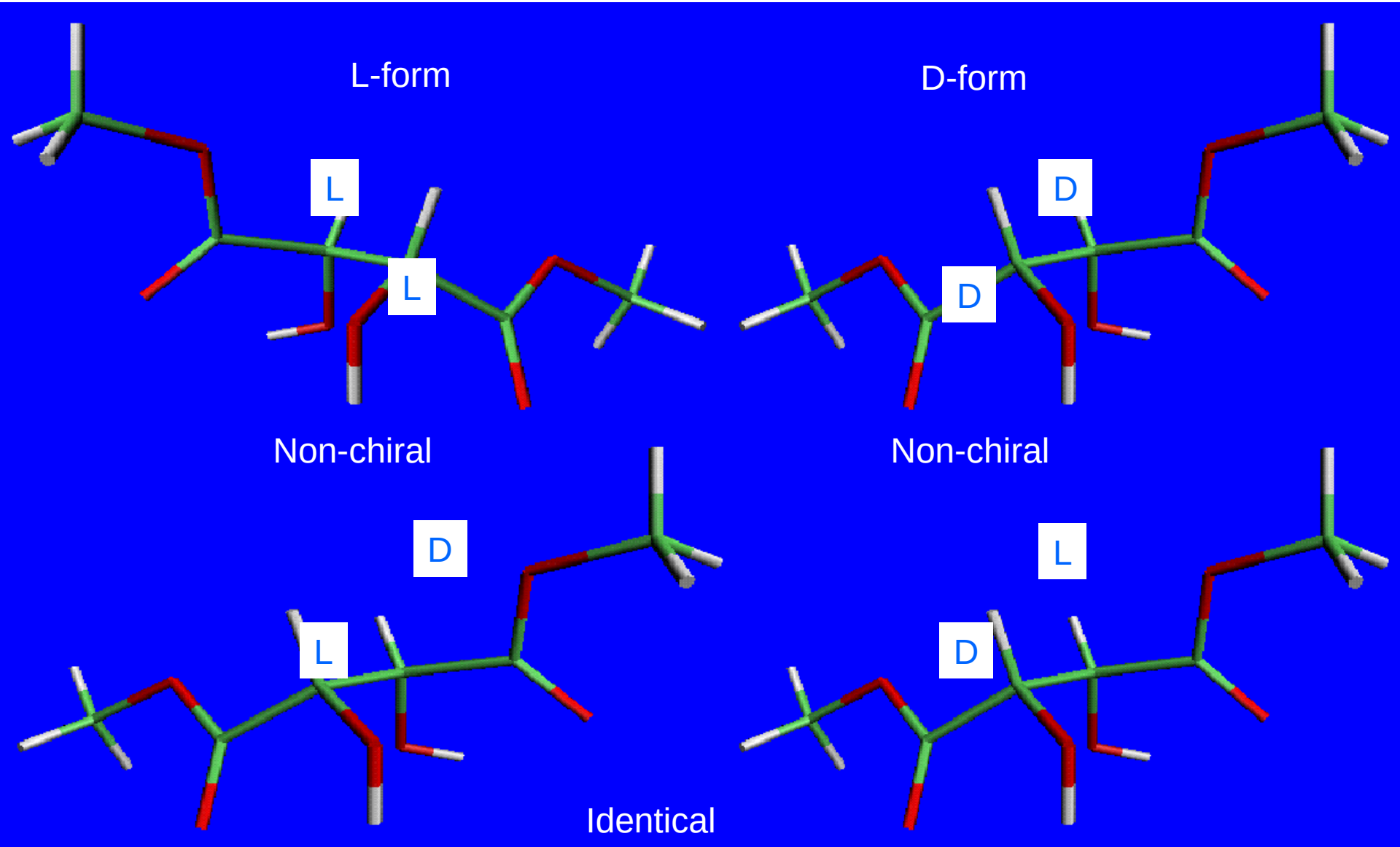
L-DMT$_d$



Both methyl groups are deuterated for the L-form to distinguish it from the D-form (6 mass units mass difference between L and D forms)



There are three possible forms of DMT molecules, corresponding to 4 combinations of chirality of two chiral carbon atoms in the molecule backbone (B3P86/3-21G* basis)



Dimer formation event sequence in chemical ionization (FT ICR trap)

Ionize. Wait for the equilibrium (10 seconds)

Eject all but monomer

Wait for dimer formation. Detect (0.1-100 seconds)

Dimer formation equilibrium in gas phase

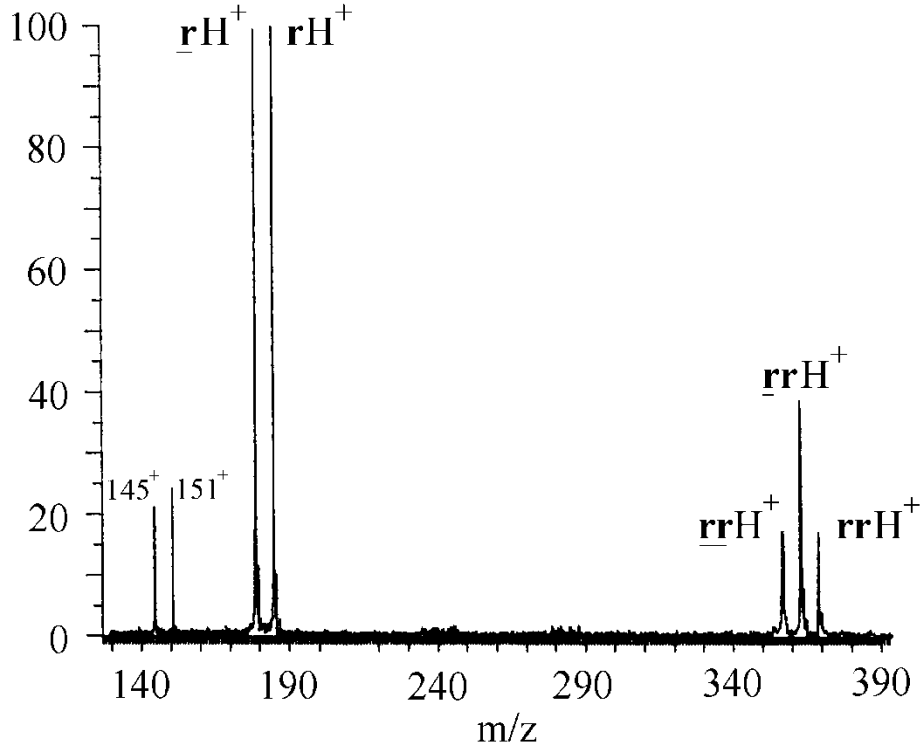
$M + e^- \rightarrow R^+ + (M\text{-}R) + 2e^-$ (ionization)

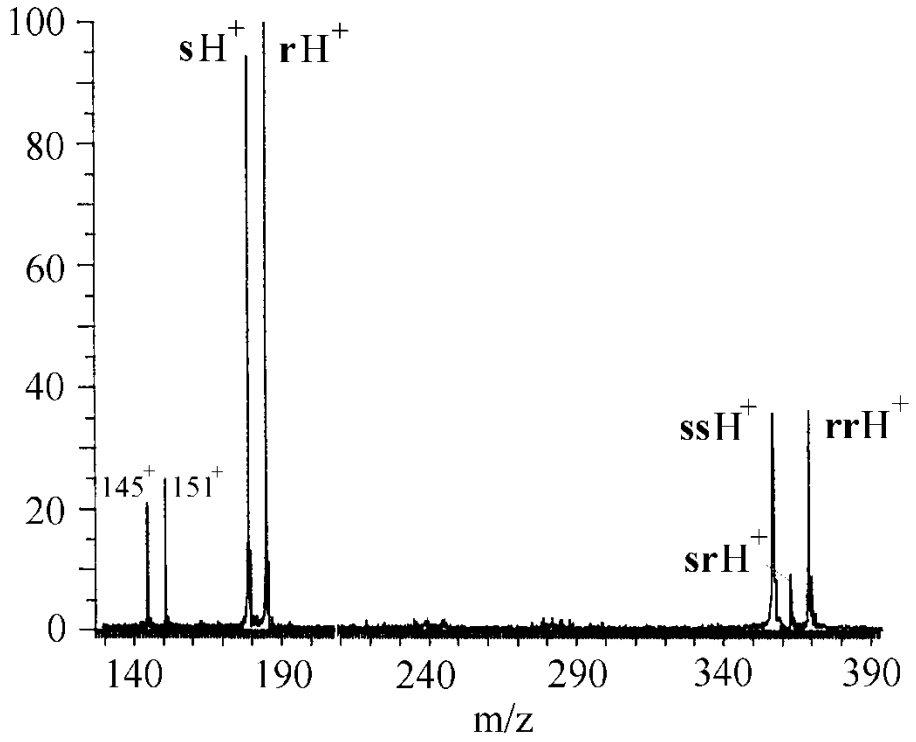
$R^+ + M \rightarrow H^+M + (R\text{-}H)$ (proton transfer)

$H^+M + M \rightleftharpoons H^+M_2^* \rightleftharpoons H^+M_2$ (dimer formation)

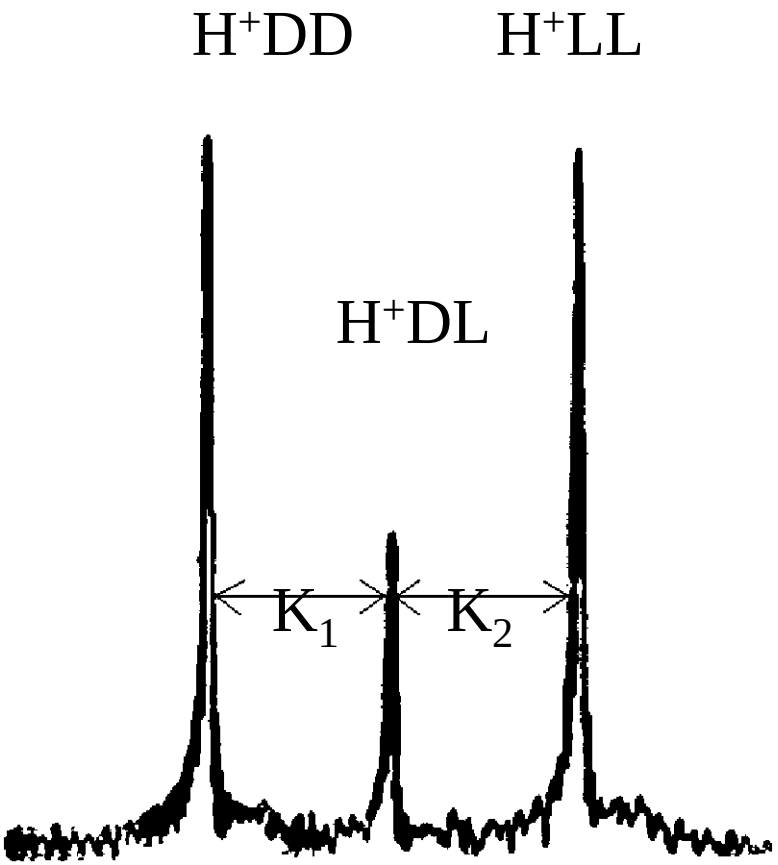
$H^+LL + D \rightleftharpoons H^+LD + L$ (ligand exchange)

CI of the mixture of dimethyltartrate of different chiral forms with one form labeled(d6). FT ICR spectra





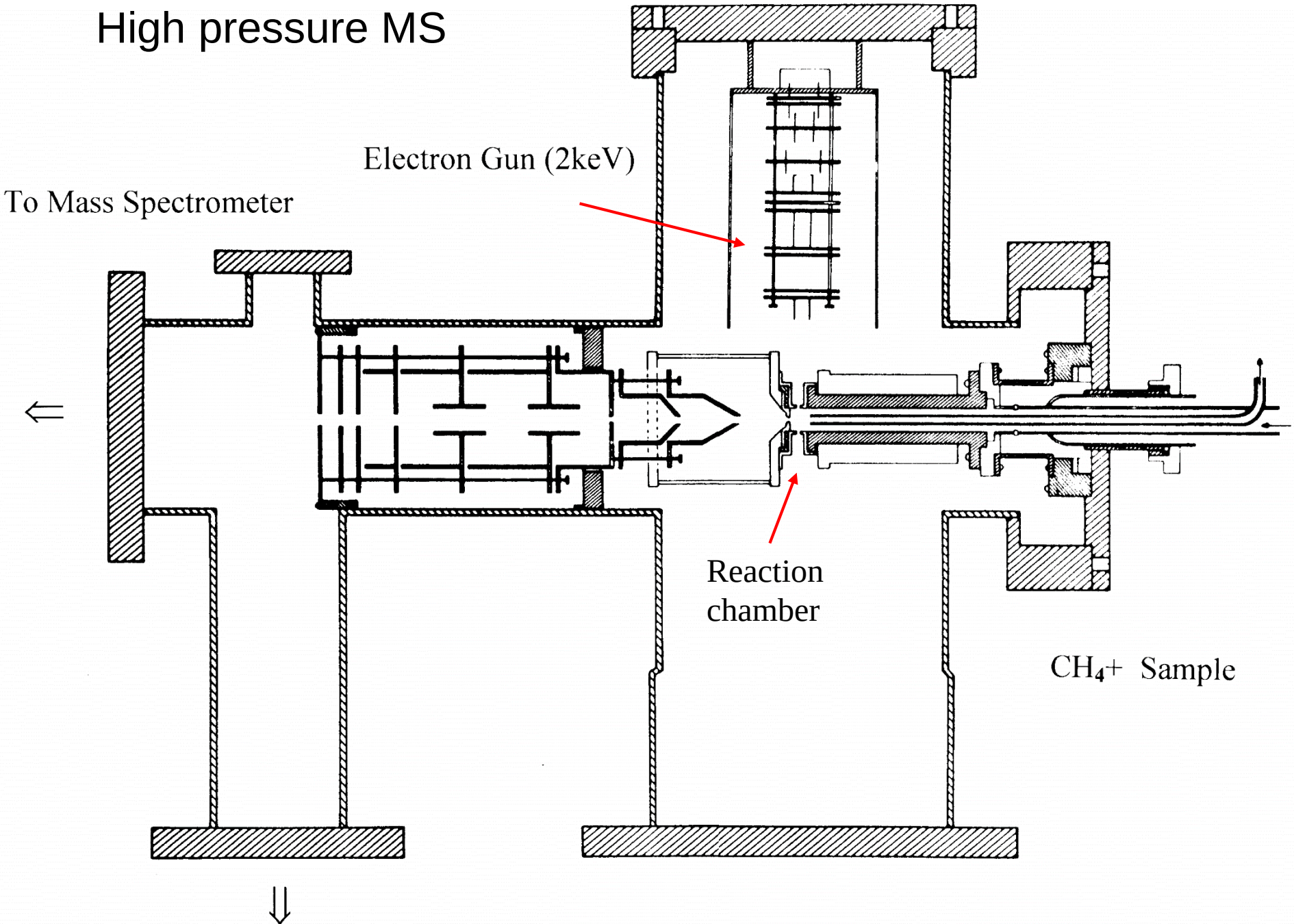
Ligand exchange equilibrium constant



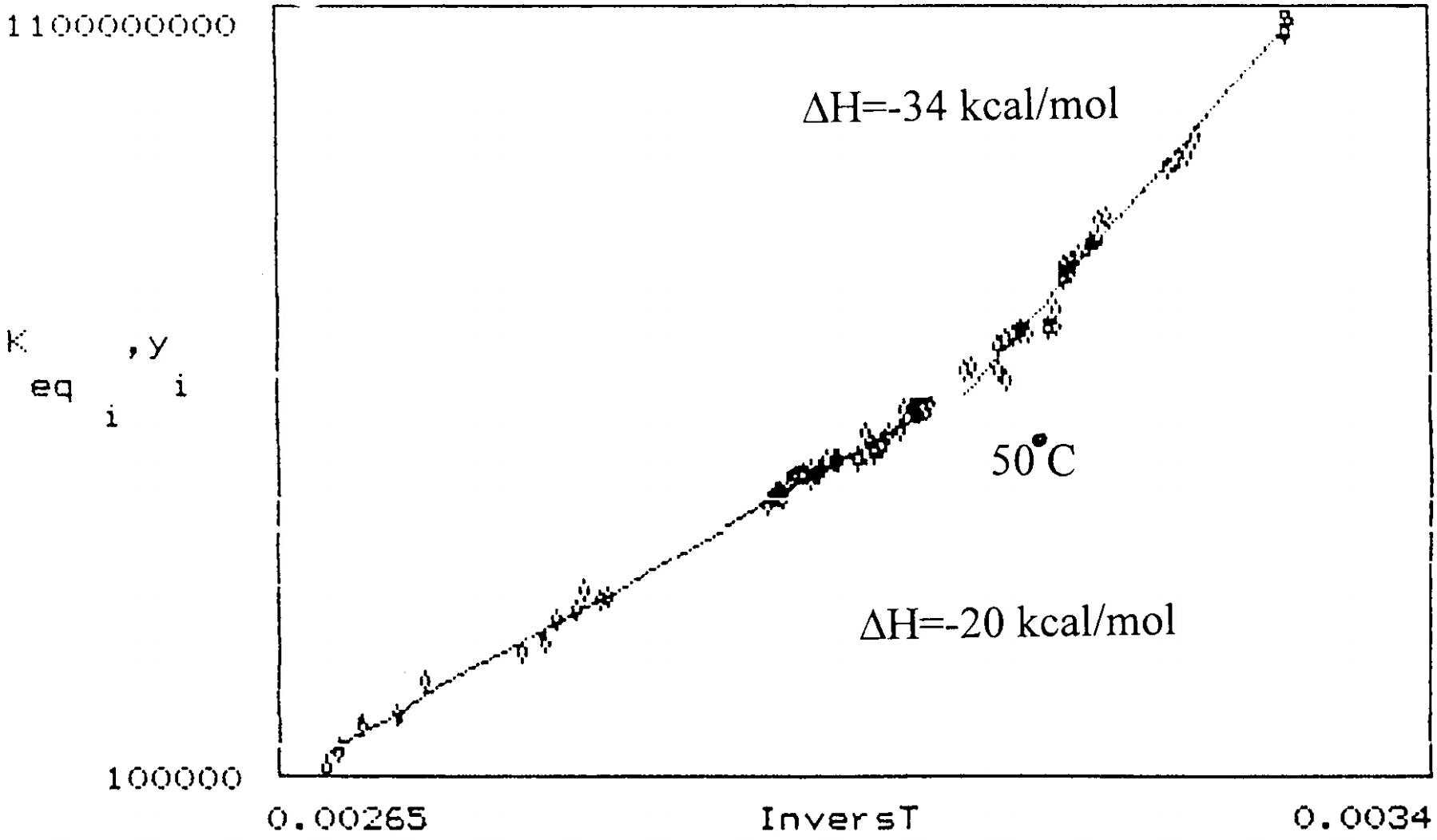
- $H^+DD + L \Leftrightarrow H^+DL + D$
- $H^+LL + D \Leftrightarrow H^+DL + L$
- $K_1=[H^+DL]*[D]/[H^+DD]*[L]$
- $K_2=[H^+DL]*[L]/[H^+LL]*[D]$
- $K_1 = K_2 = K$
- $[H^+DL]/[H^+DD]*[H^+LL]$

$$\Delta\Delta F=-RT*\ln K$$

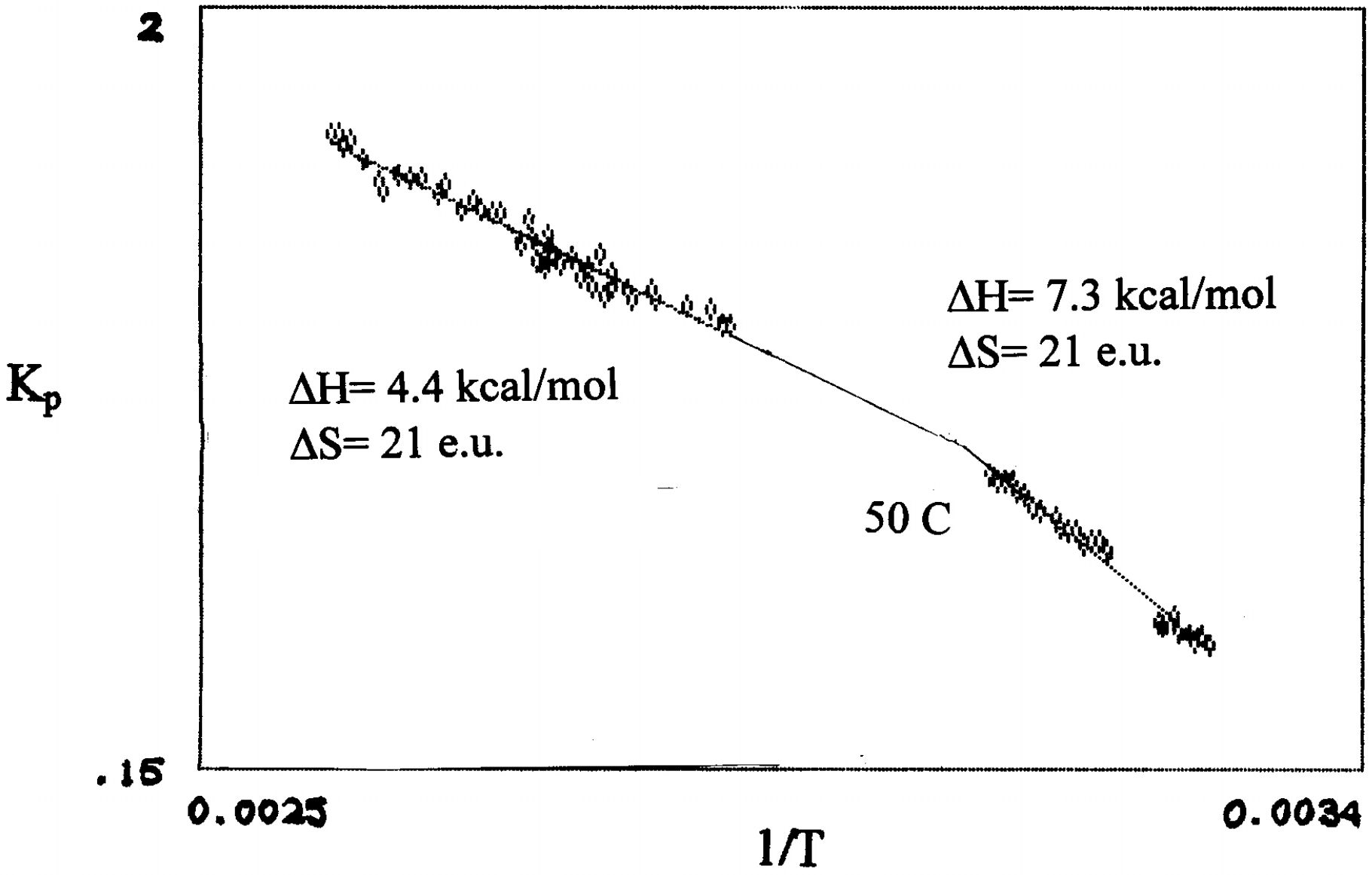
High pressure MS



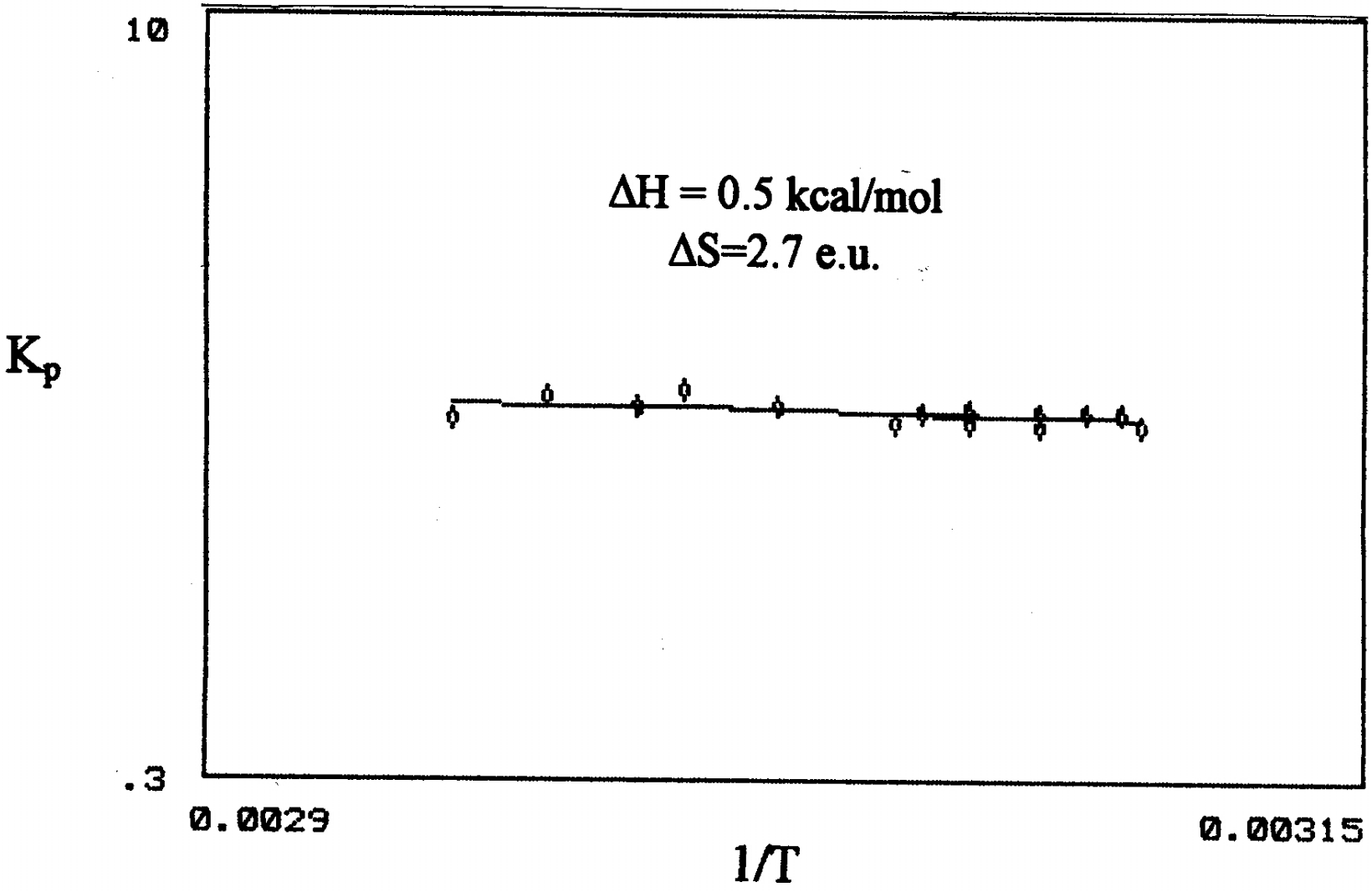
$H^+M + M \rightarrow H^+M_2$ M= DMT

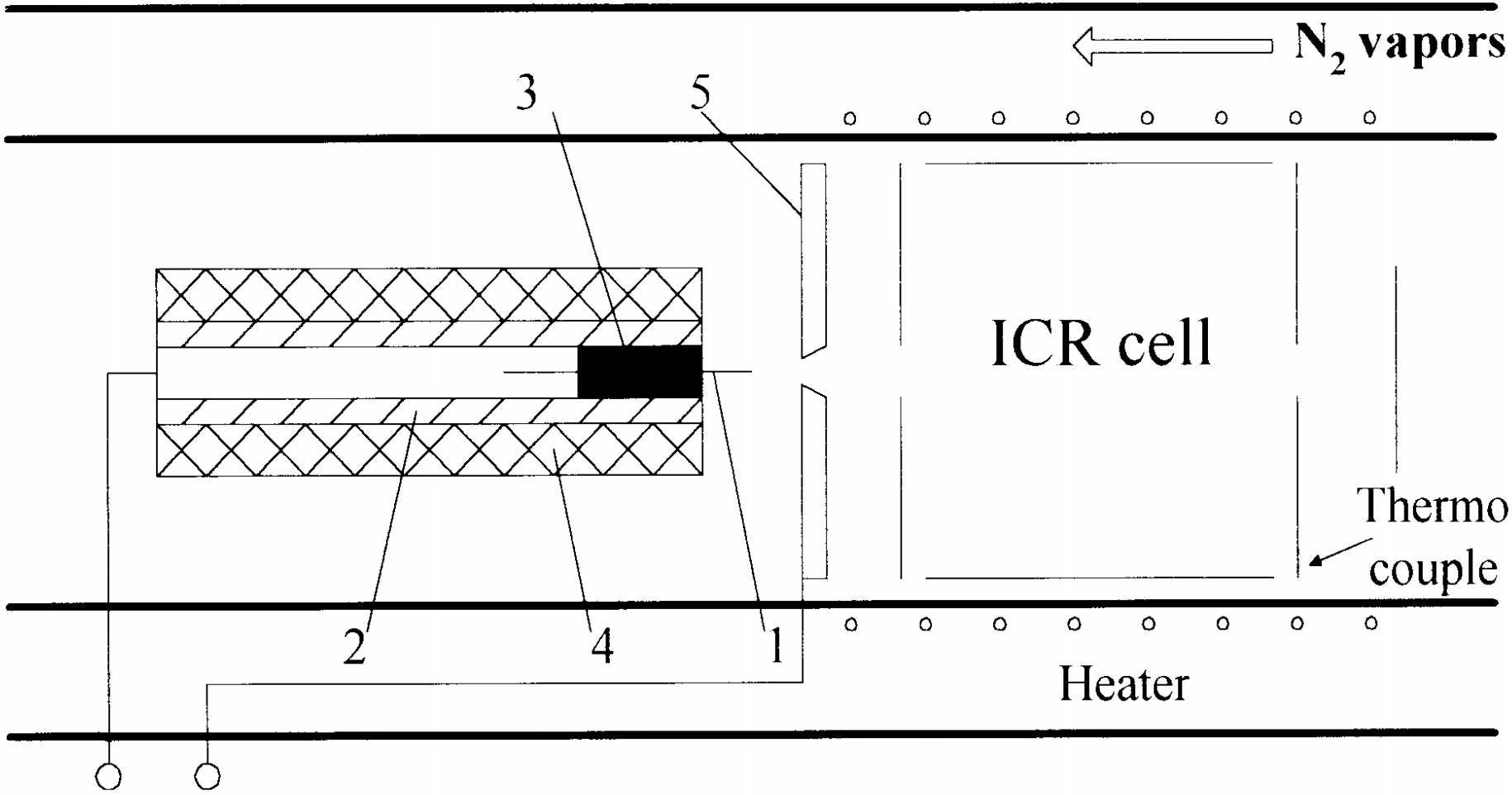


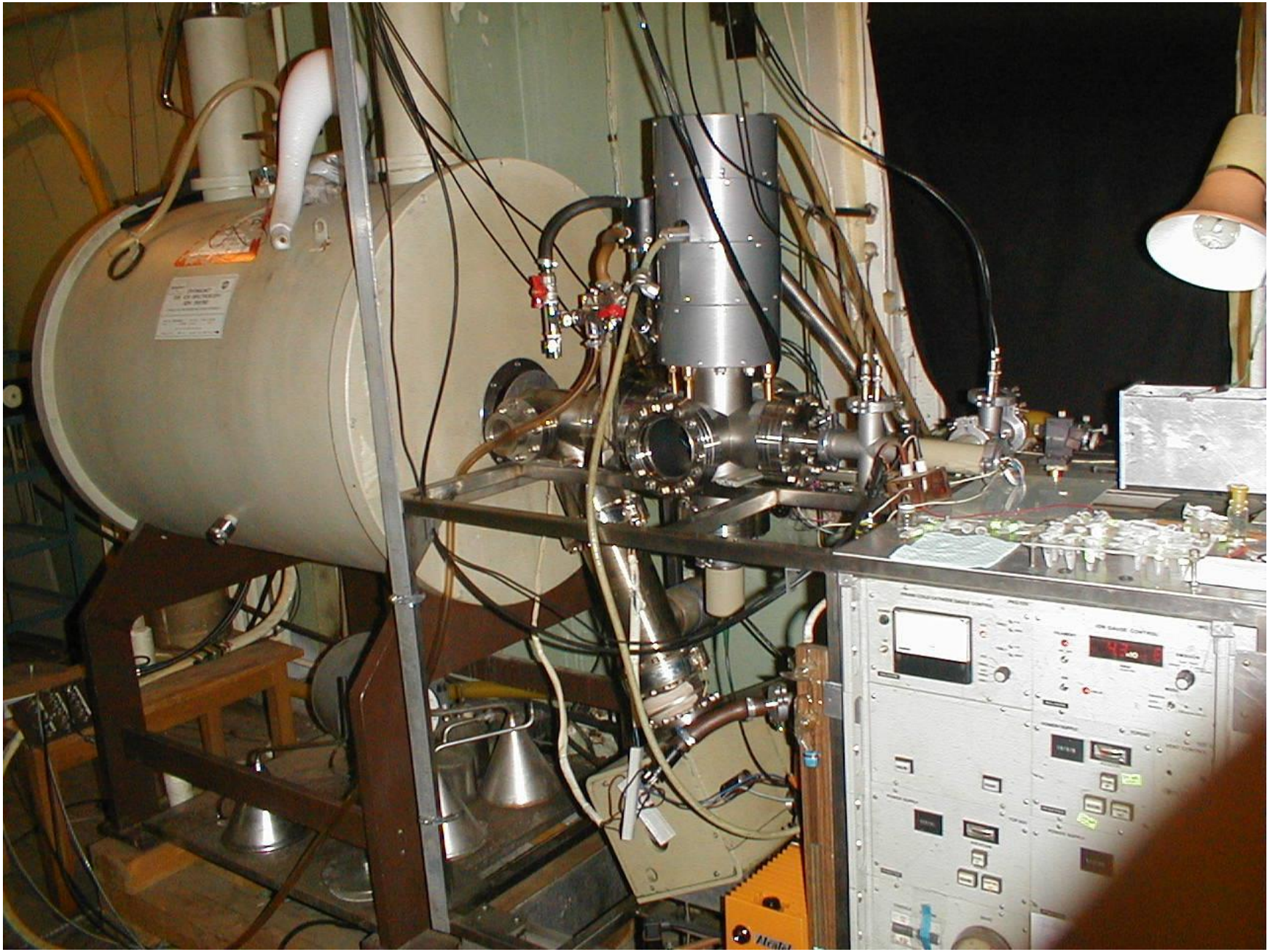
$H^+LD + L \rightarrow H^+L_2$ L and D are DMT enantiomers



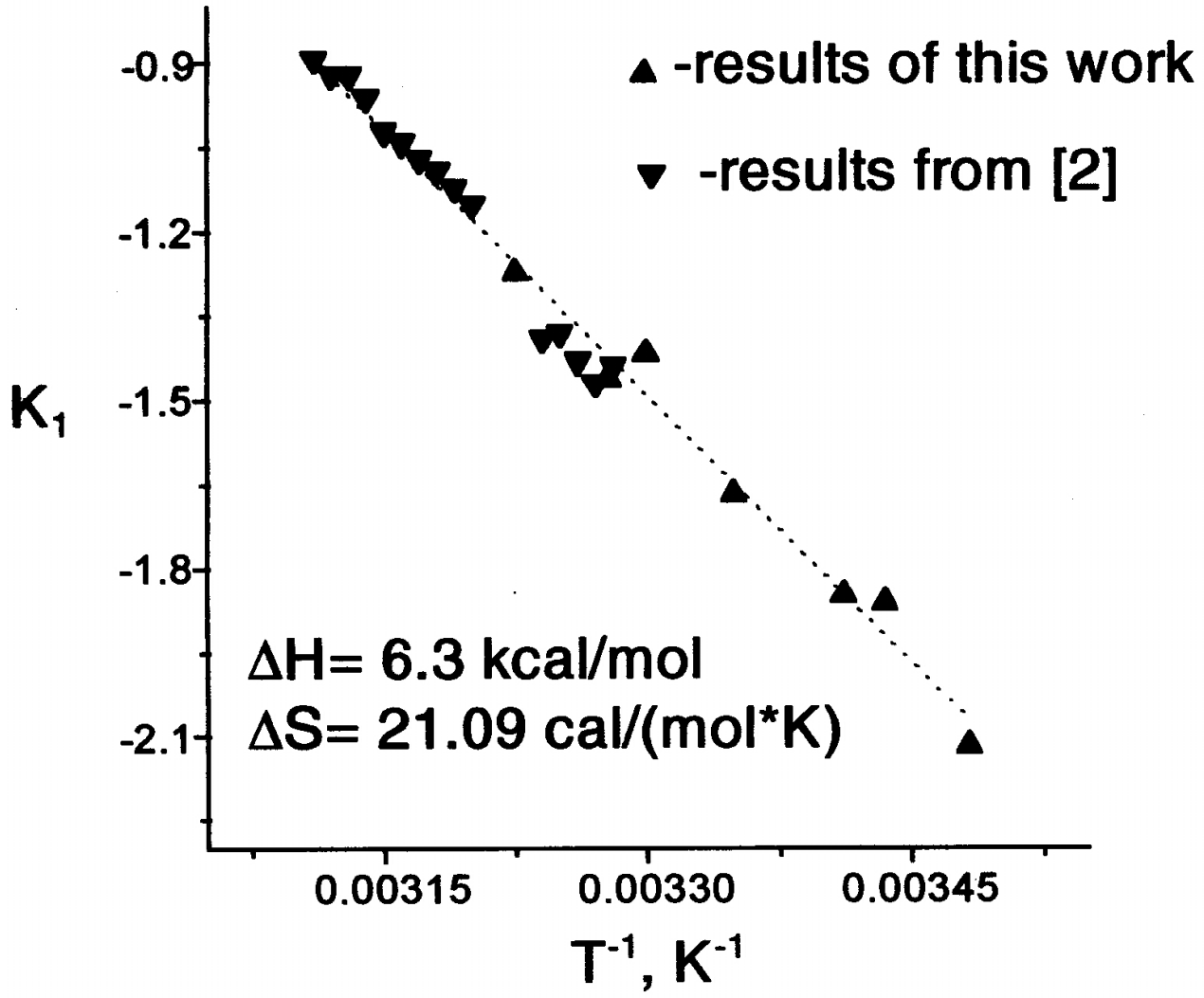
$Li^+LD + L \rightarrow Li^+L_2$ L and D are DMT enantiomers




N2 vapors
3
5
ICR cell
Thermo
couple
2
4
1
Heater

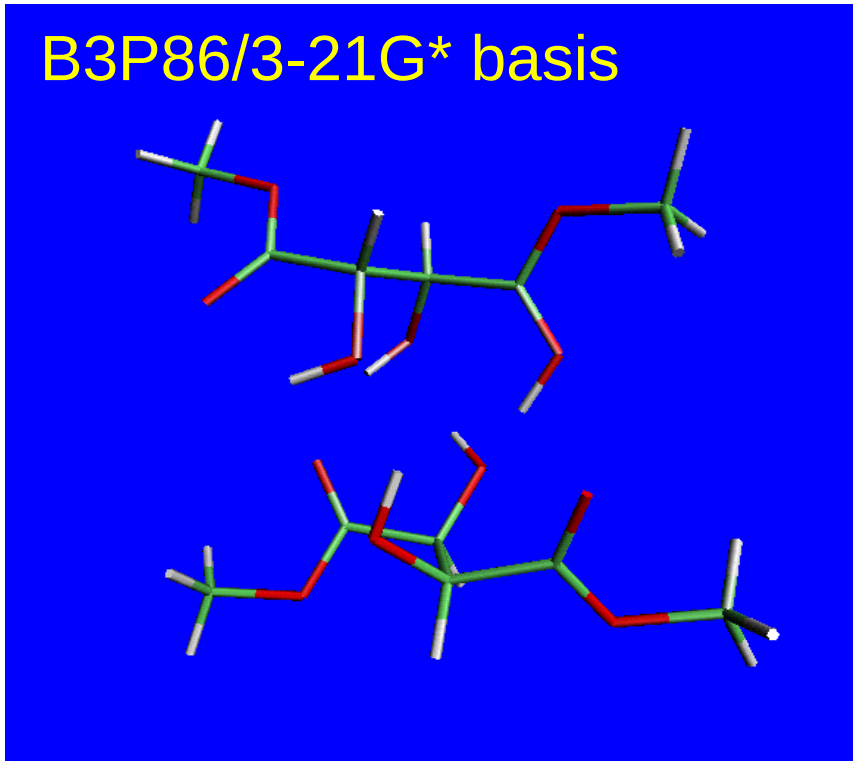


$H^+LD + L \rightarrow H^+L_2$ L and D are DMT enantiomers

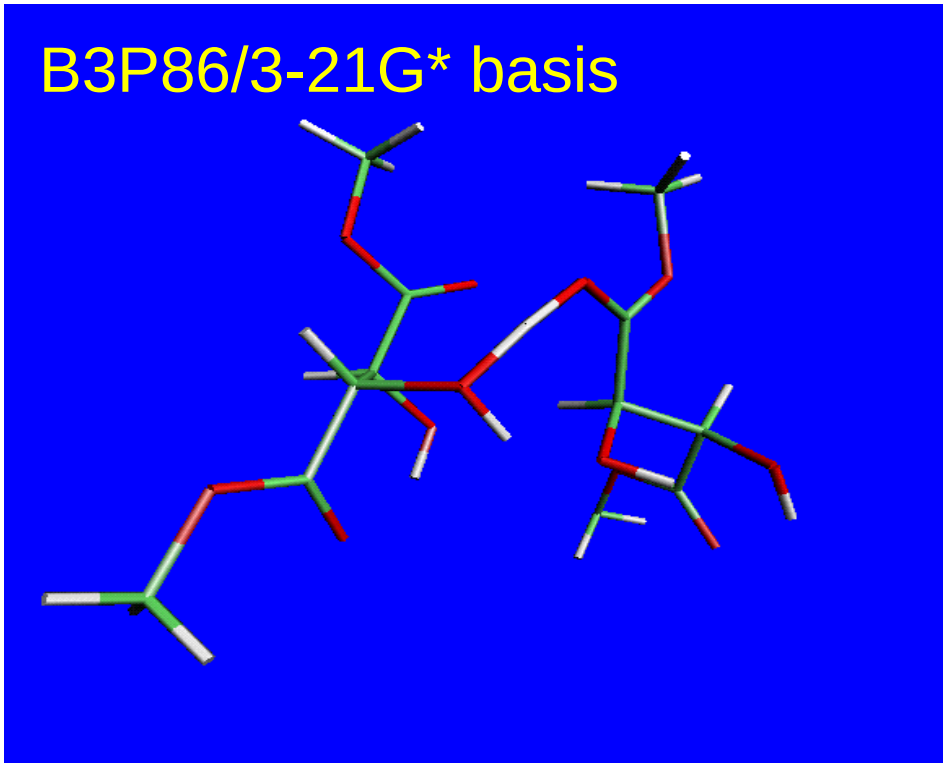


The nature of molecular chiral recognition In protonated DMT dimers

H^+Dimethyltartrate DD-dimer



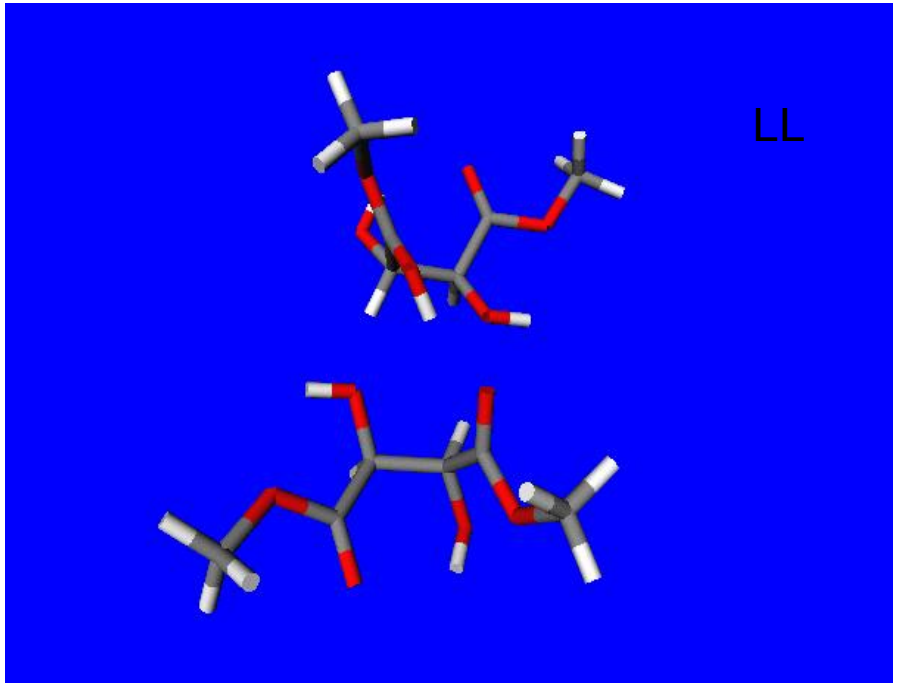
H^+Dimethyltartrate DL-dimer

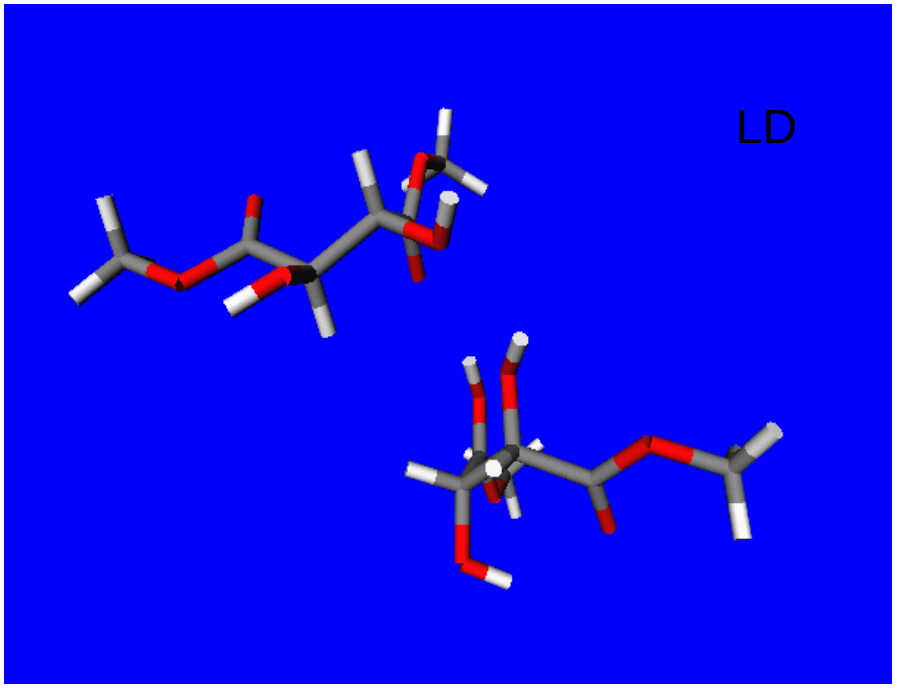


5.2 kcal/mole

$H^+(DMT)_2$ group

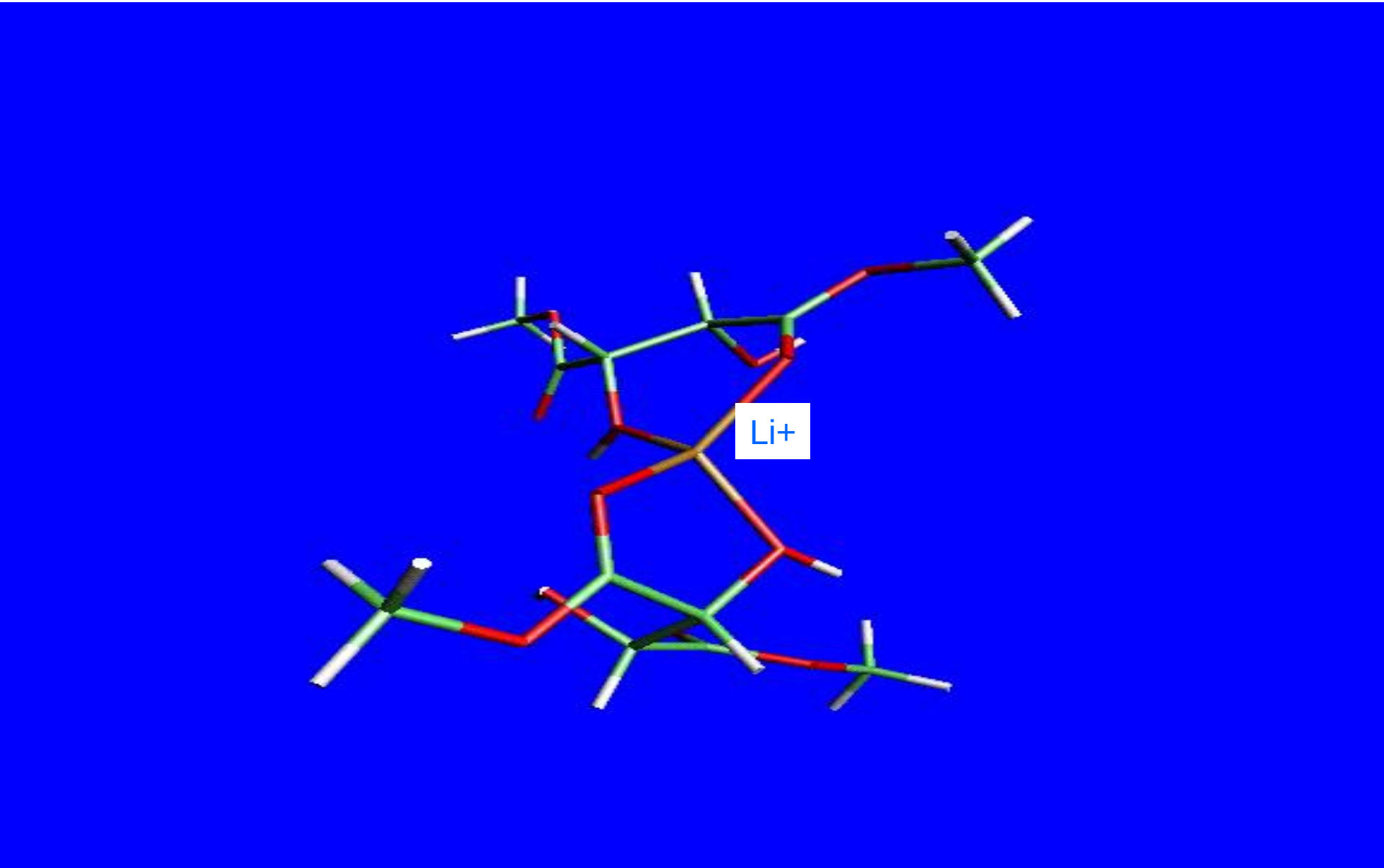
Ab initio Becke,Lee,Yang,Parr Method in 6-311G* bases



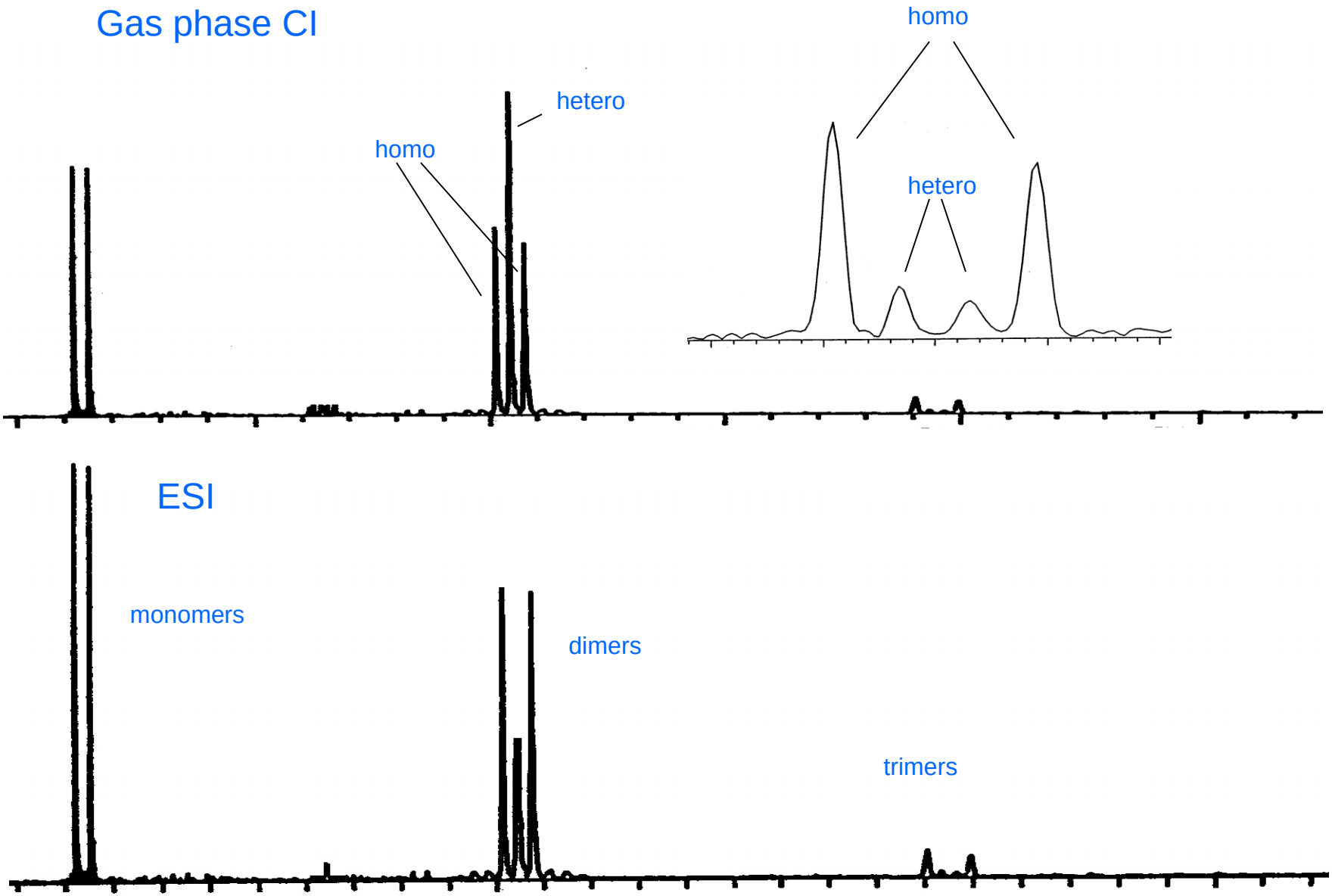


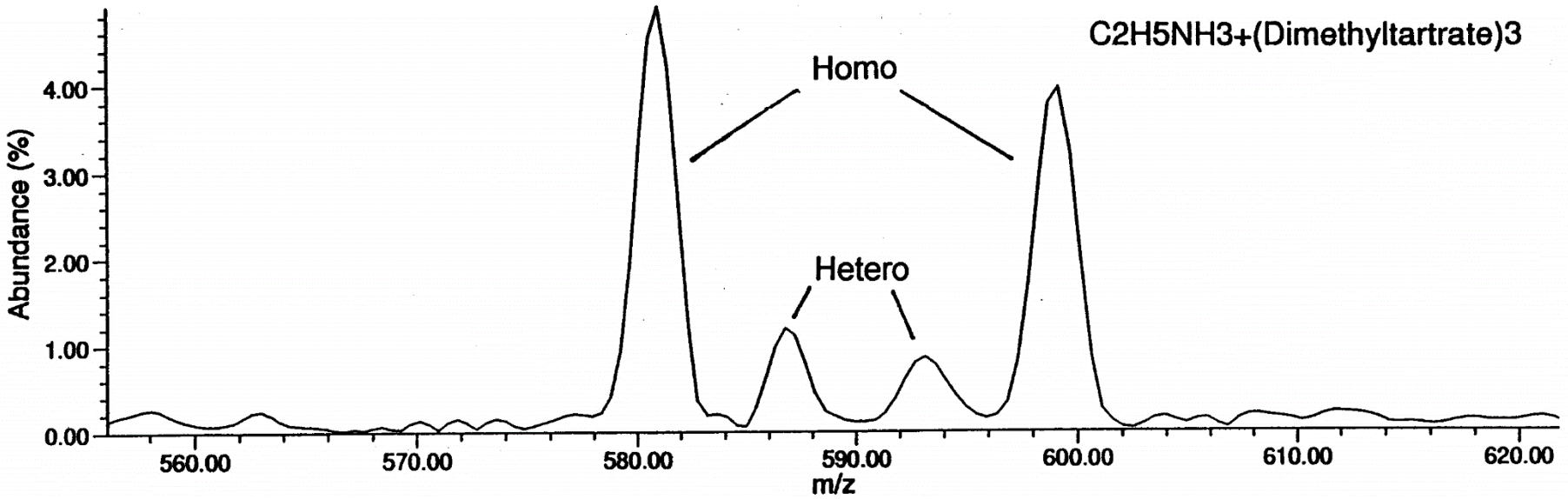
6.81 kcal/mole

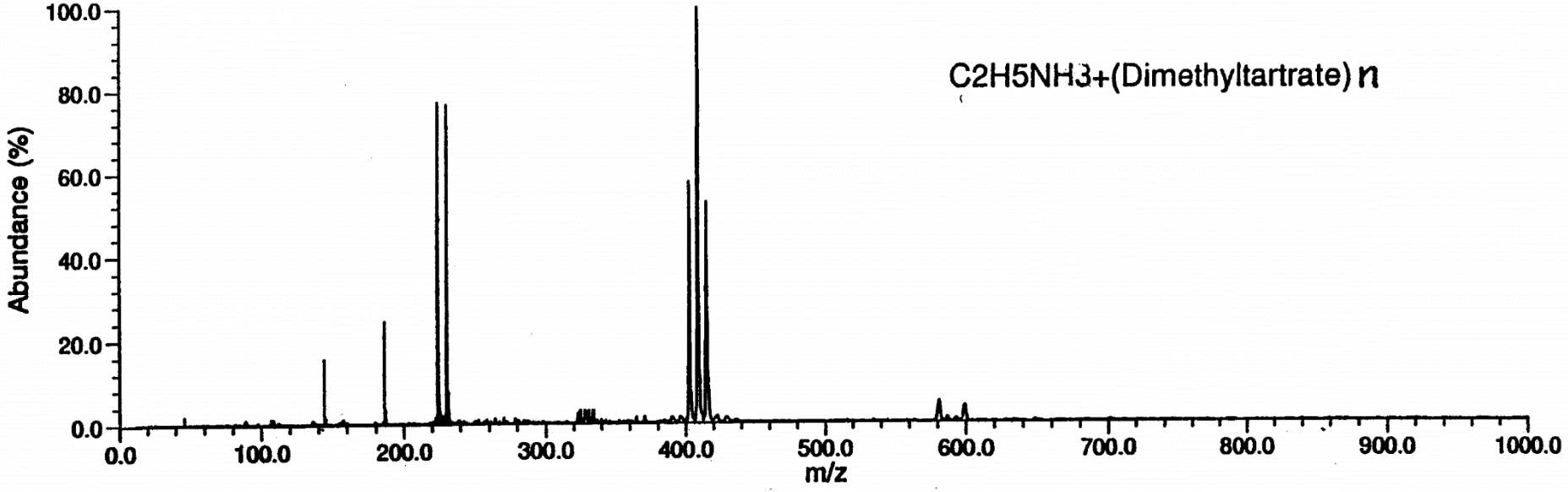
$Li^{+}(DMT)_2$ (B3P86/3-21G* basis)



FT ICR spectra of Na^+ based DMT clusters

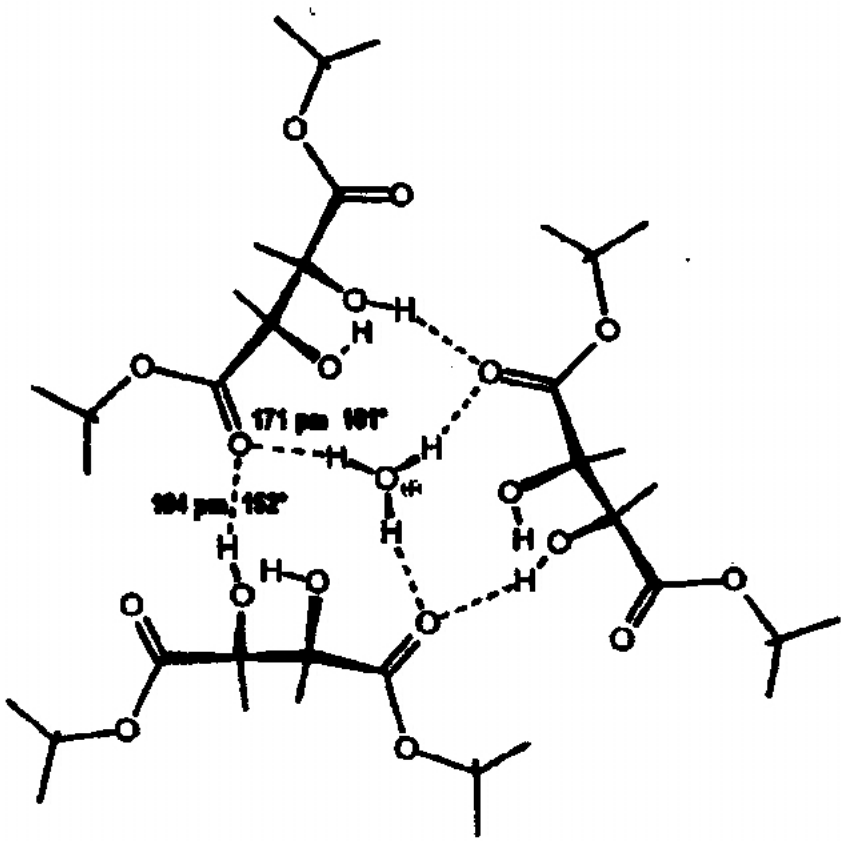



C2H5NH3+(Dimethyltartrate)3
Homo
Hetero
Abundance (%)
4.00
3.00
2.00
1.00
0.00
560.00
570.00
580.00
590.00
600.00
610.00
620.00
m/z

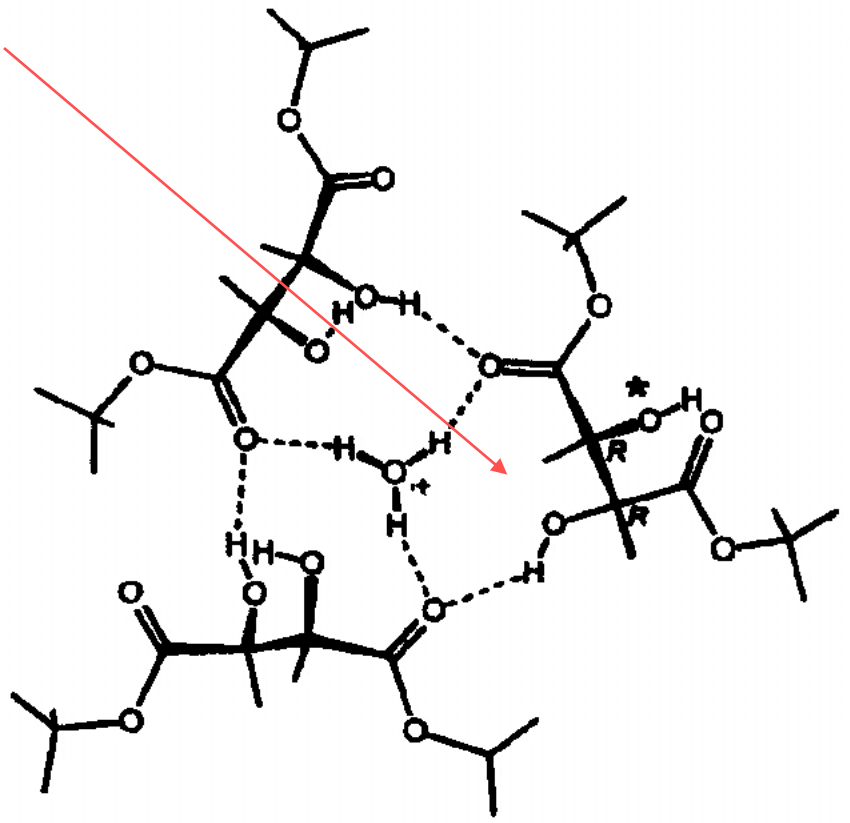

C2H5NH3+(Dimethyltartrate) n
Abundance (%)
100.0
80.0
60.0
40.0
20.0
0.0
0.0
100.0
200.0
300.0
400.0
500.0
600.0
700.0
800.0
900.0
1000.0
m/z

The nature of molecular chiral recognition in protonated DMT trimers (propellers)

No H-bond!



sss·H_3O^+



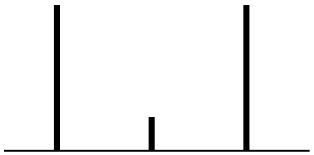
ssr·H_3O^+

Possible distribution of peak intensities in dimer and trimer groups

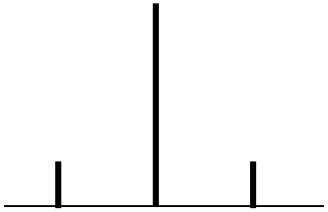
Dimers

Statistical
1:2:1

Homo
dominates

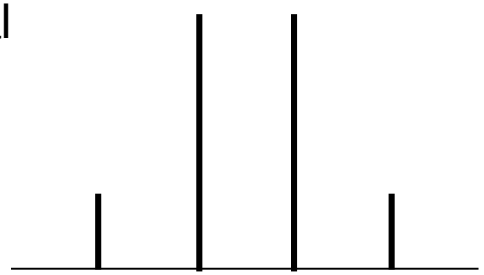


Hetero
dominates

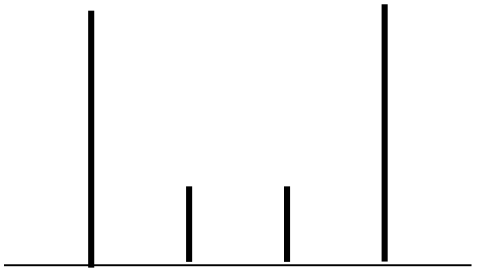


Trimers

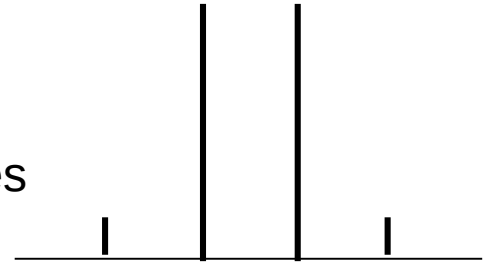
Statistical
1:3:3:1



Homo
dominates



Hetero
dominates

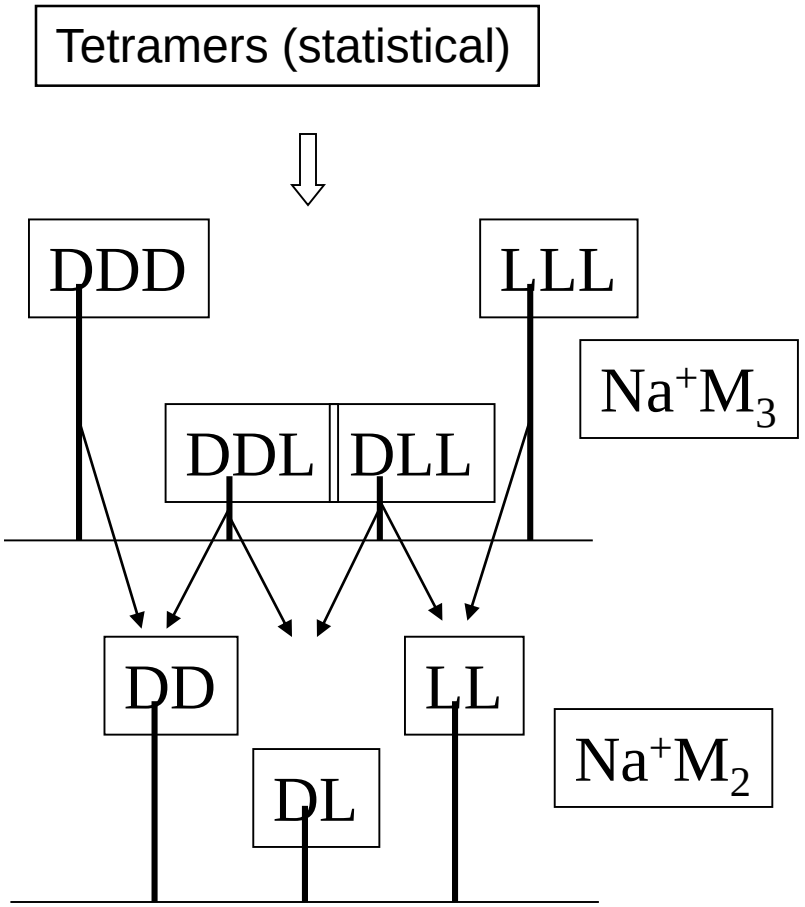


Chiral discrimination in the decay processes

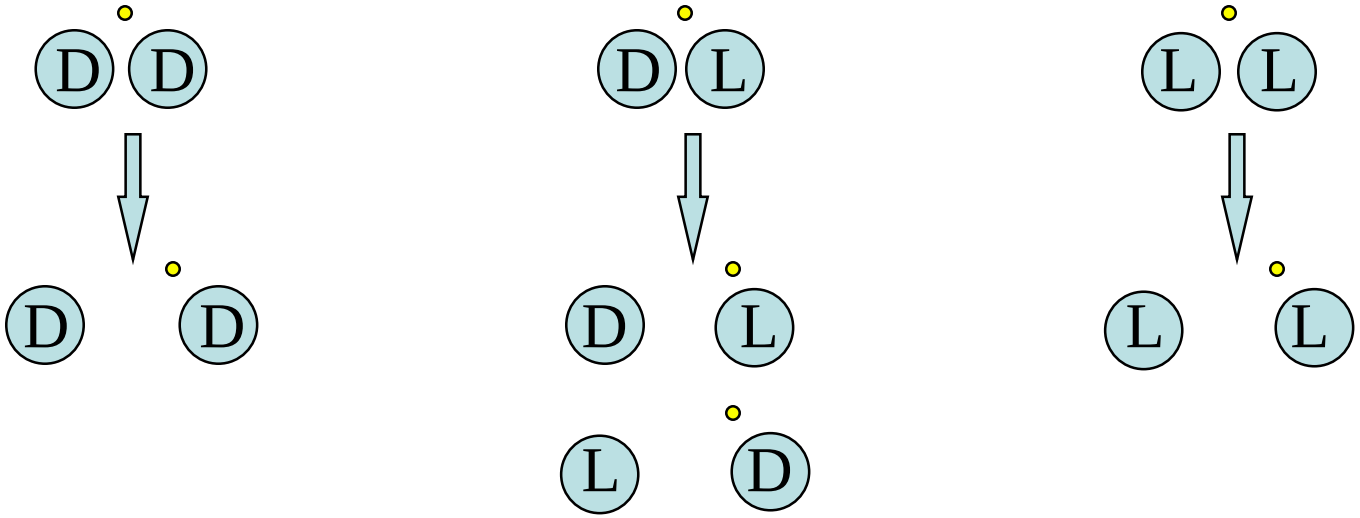
Tetramers (statistical)

Trimers (non-statistical)

Dimers (non-statistical)



Protonated dimer decay



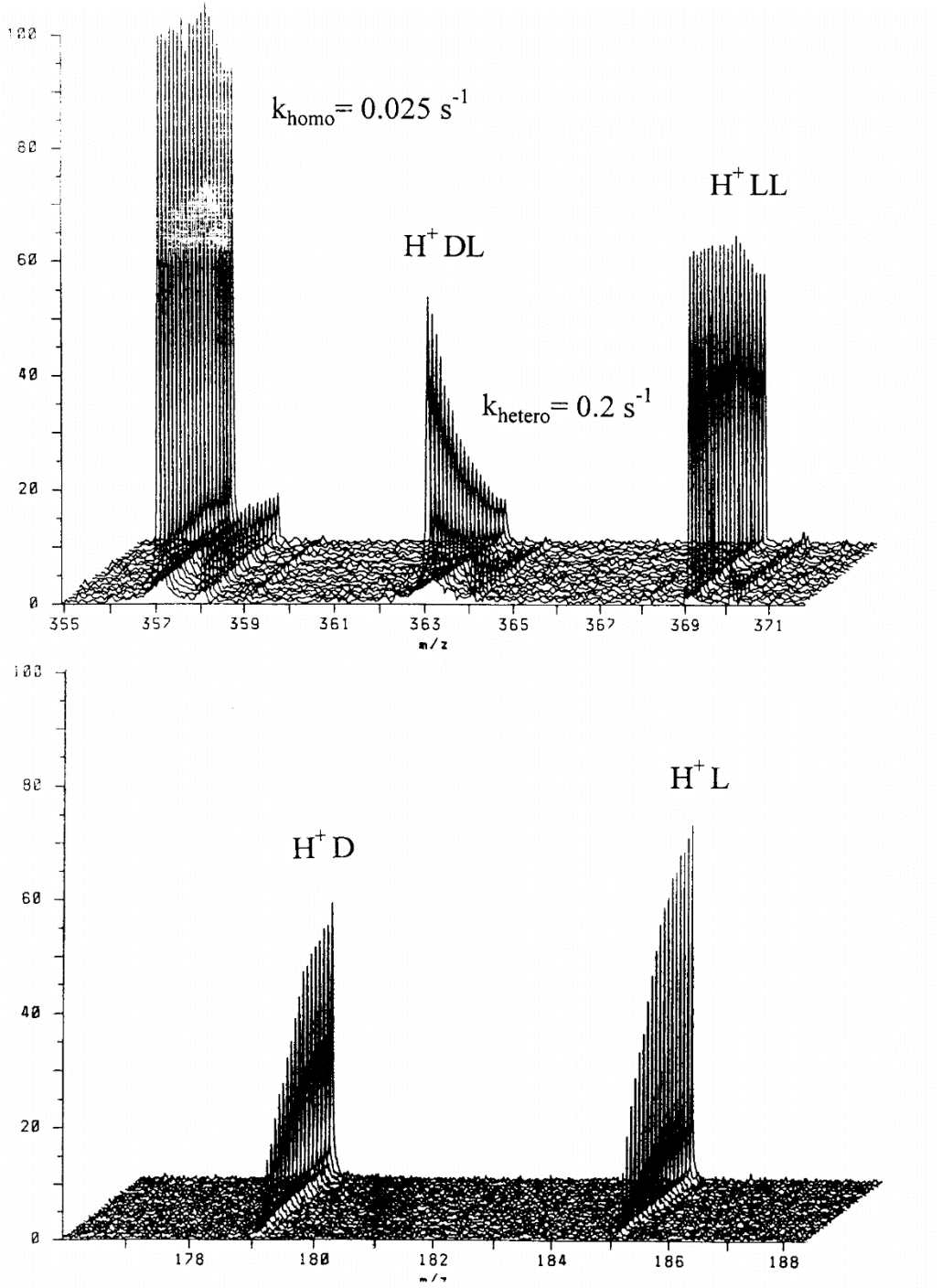
slow fast slow

Dimer decomposition event sequence

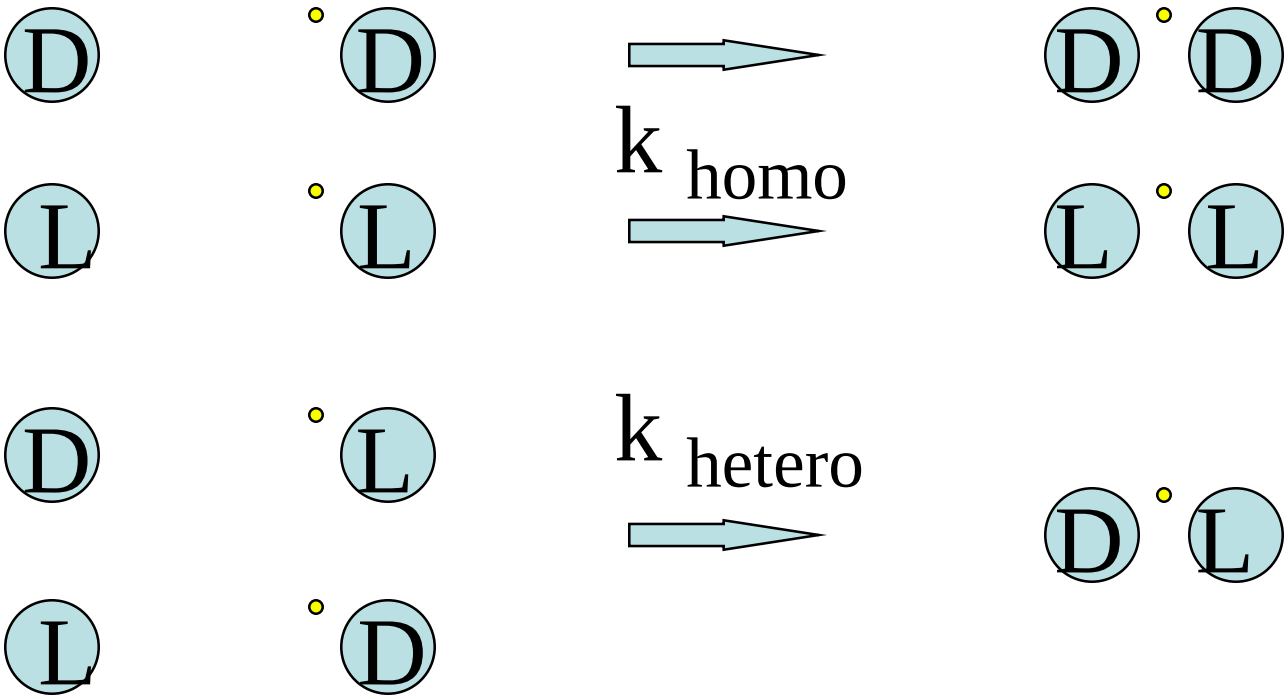
Ionize. Wait for the equilibrium (10 seconds)

Eject all but dimers

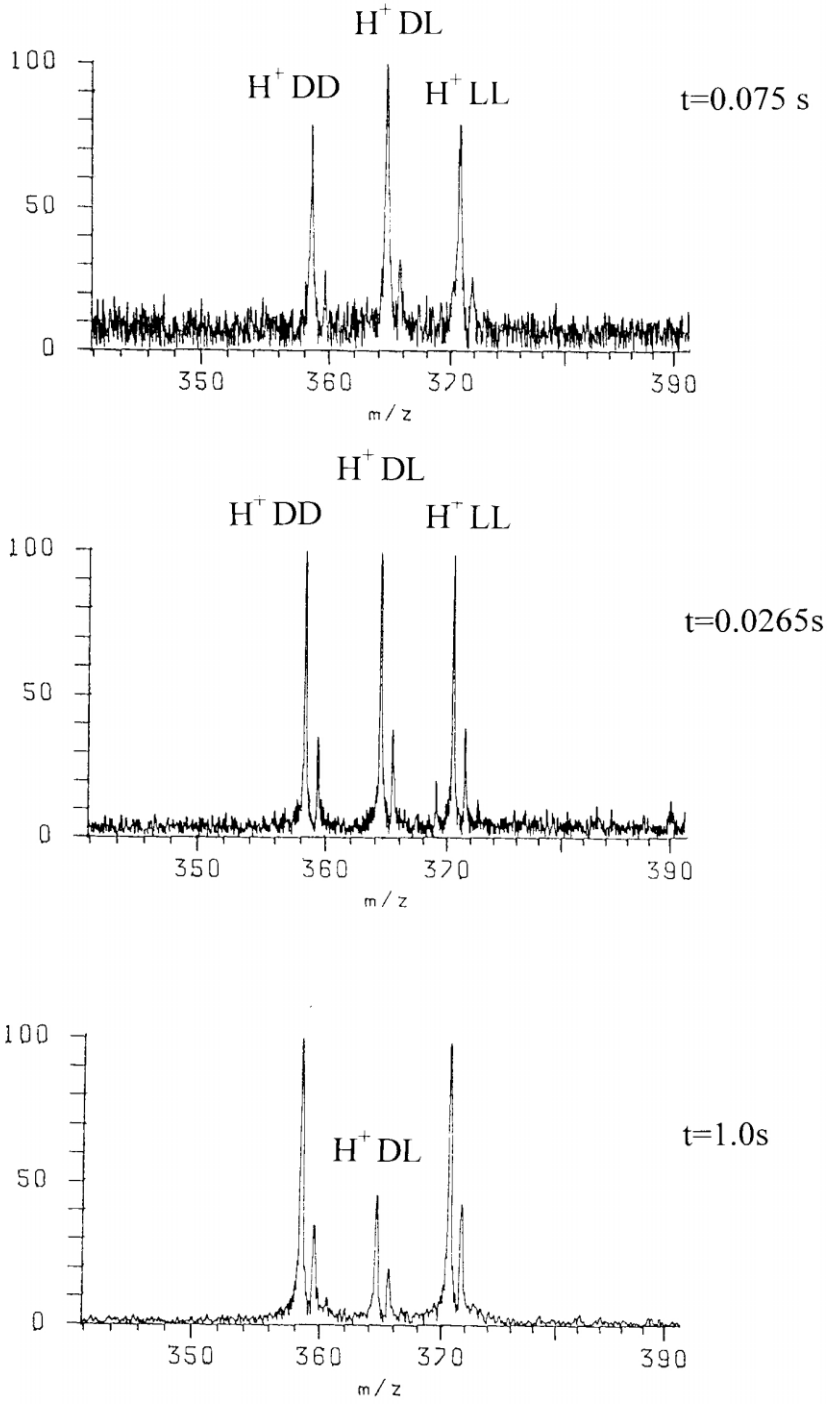
Wait for decomposition. Detect (0.1-100 seconds)

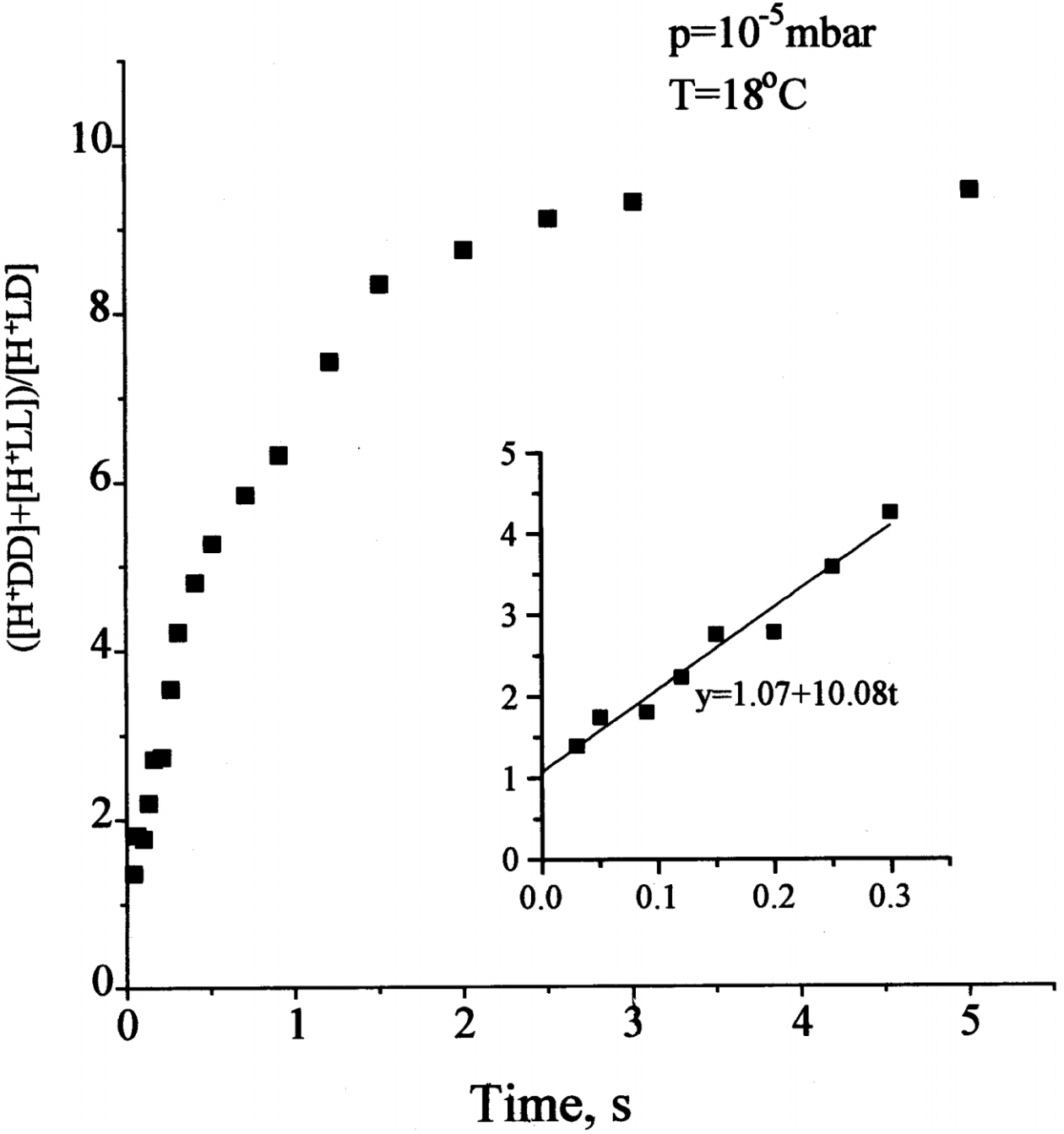

k_{homo}= 0.025 s^{-1}
H^+ LL
H^+ DL
k_{hetero}= 0.2 s^{-1}
100
80
60
40
20
0
355
357
359
361
363
365
367
369
371
m/z
H^+ L
H^+ D
178
180
182
184
186
188

Dimer formation



Is k_{homo} equal to k_{hetero} ?

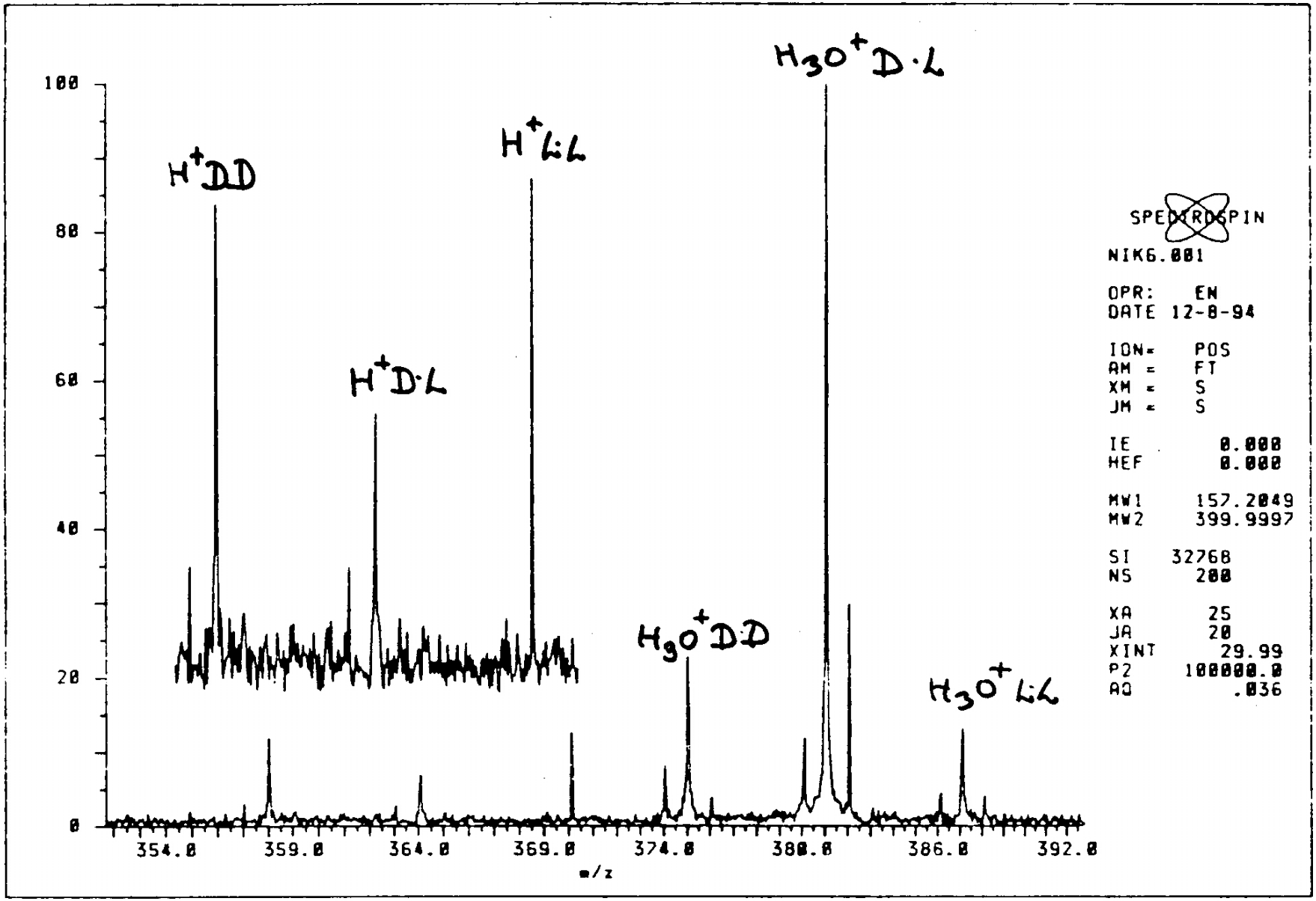

H+ DL
H+ DD
H+ LL
t=0.075 s
100
50
0
350
360
370
390
m/z
H+ DL
H+ DD
H+ LL
t=0.0265s
100
50
0
350
360
370
390
m/z
100
50
0
H+ DL
t=1.0s
350
360
370
390
m/z


p=10^-5 mbar
T=18°C
([H+DD]+[H+LL])/[H+LD]
Time, s
y=1.07+10.08t
0
2
4
6
8
10
0
1
2
3
4
5
0.0
0.1
0.2
0.3

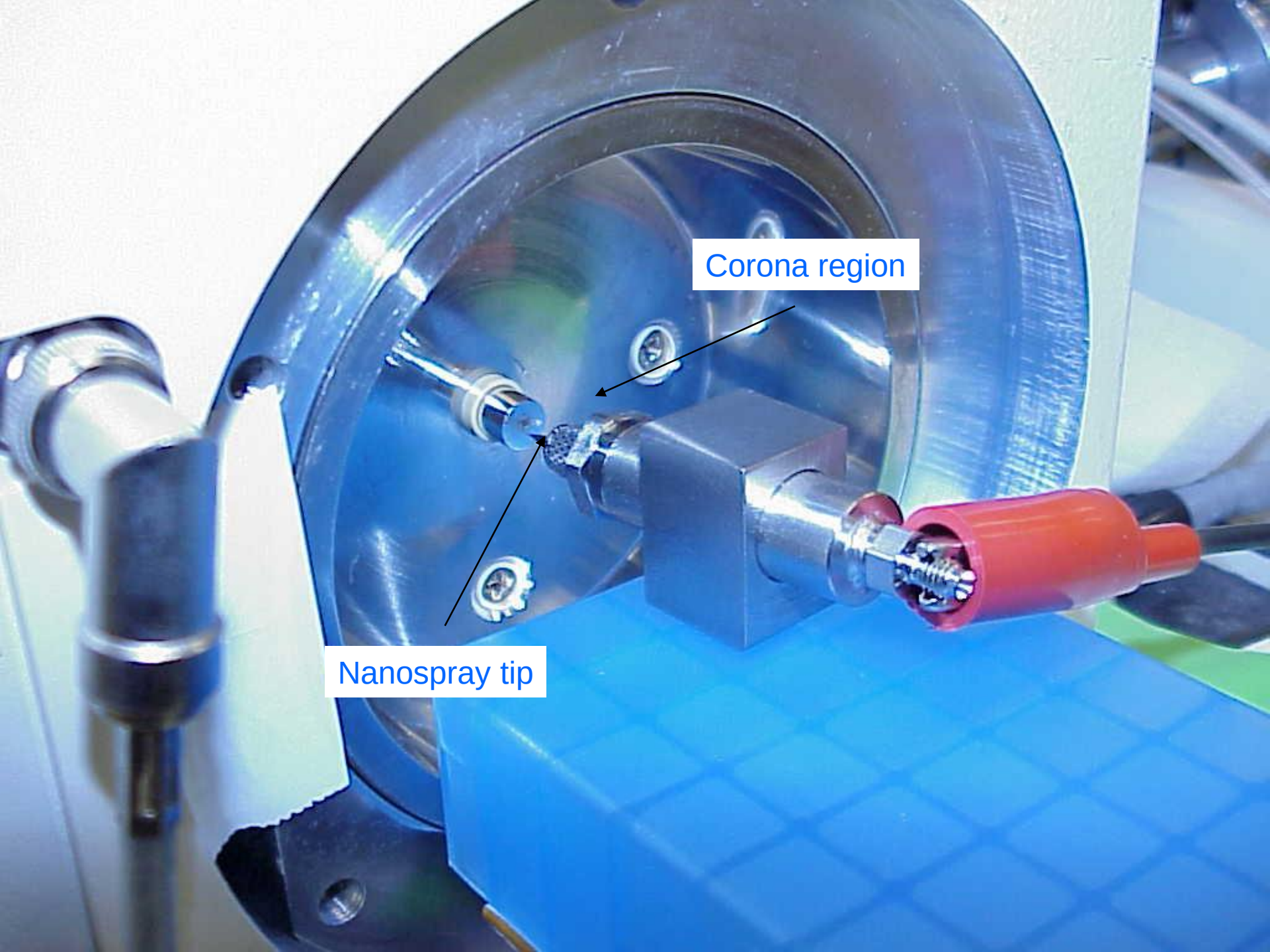
Influence of hydration on chiral recognition

Is chirality influence on dimer stability the same in absence and presence of water molecules in clusters???

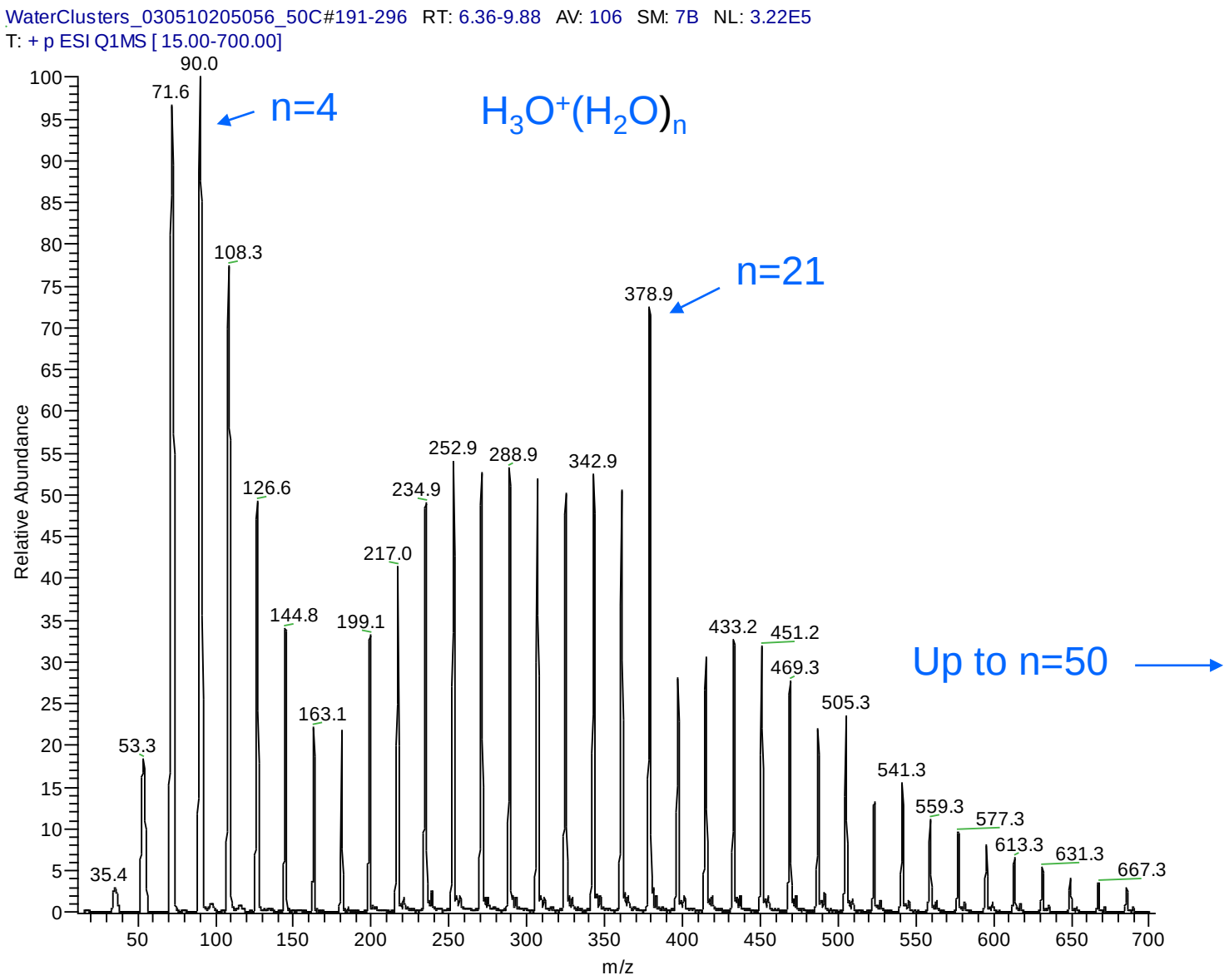
High pressure CI + FT ICR, Nikolaev, McMahon 1994 (unpublished data)

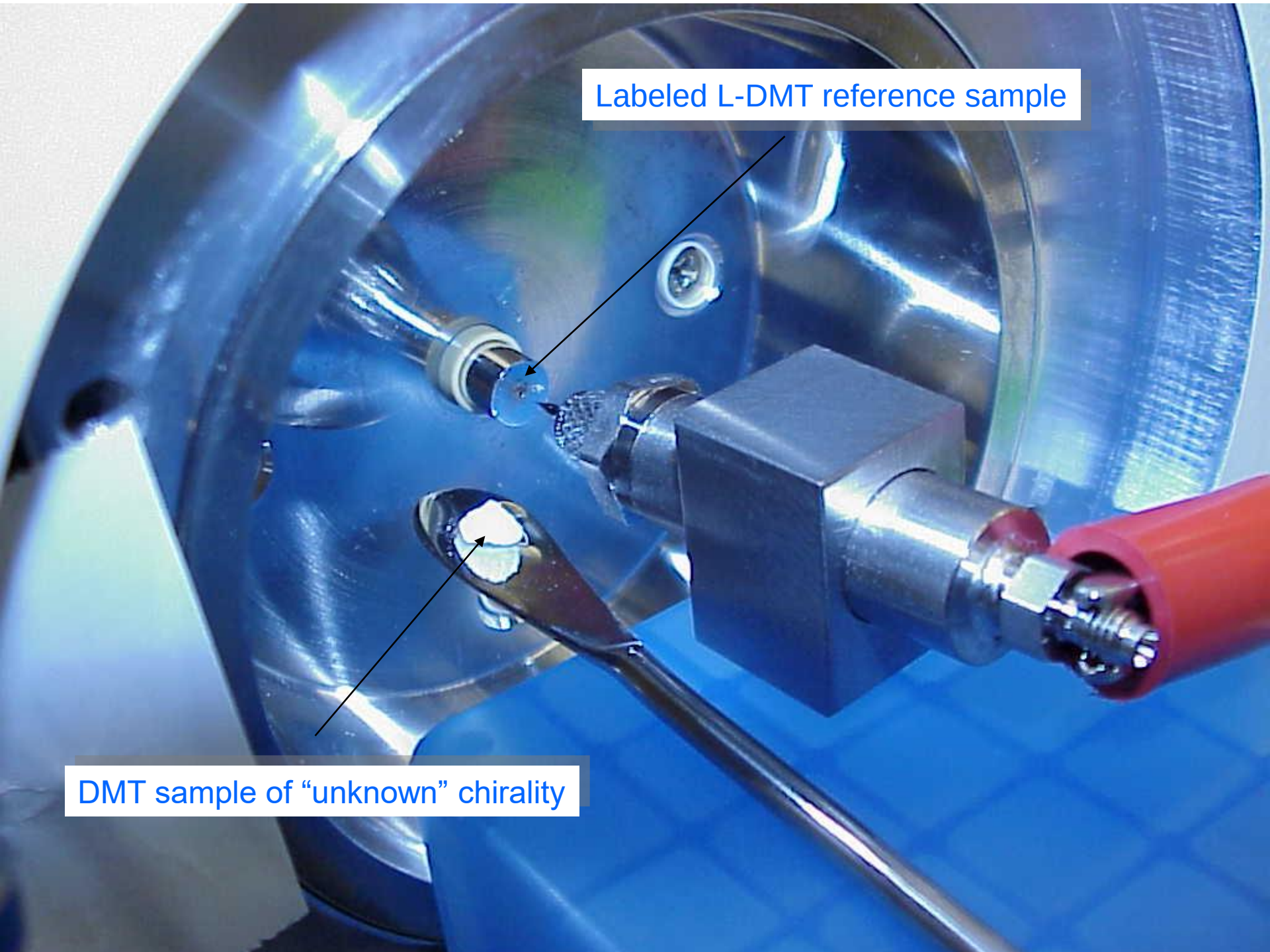


How to add water molecules to DMT clusters?

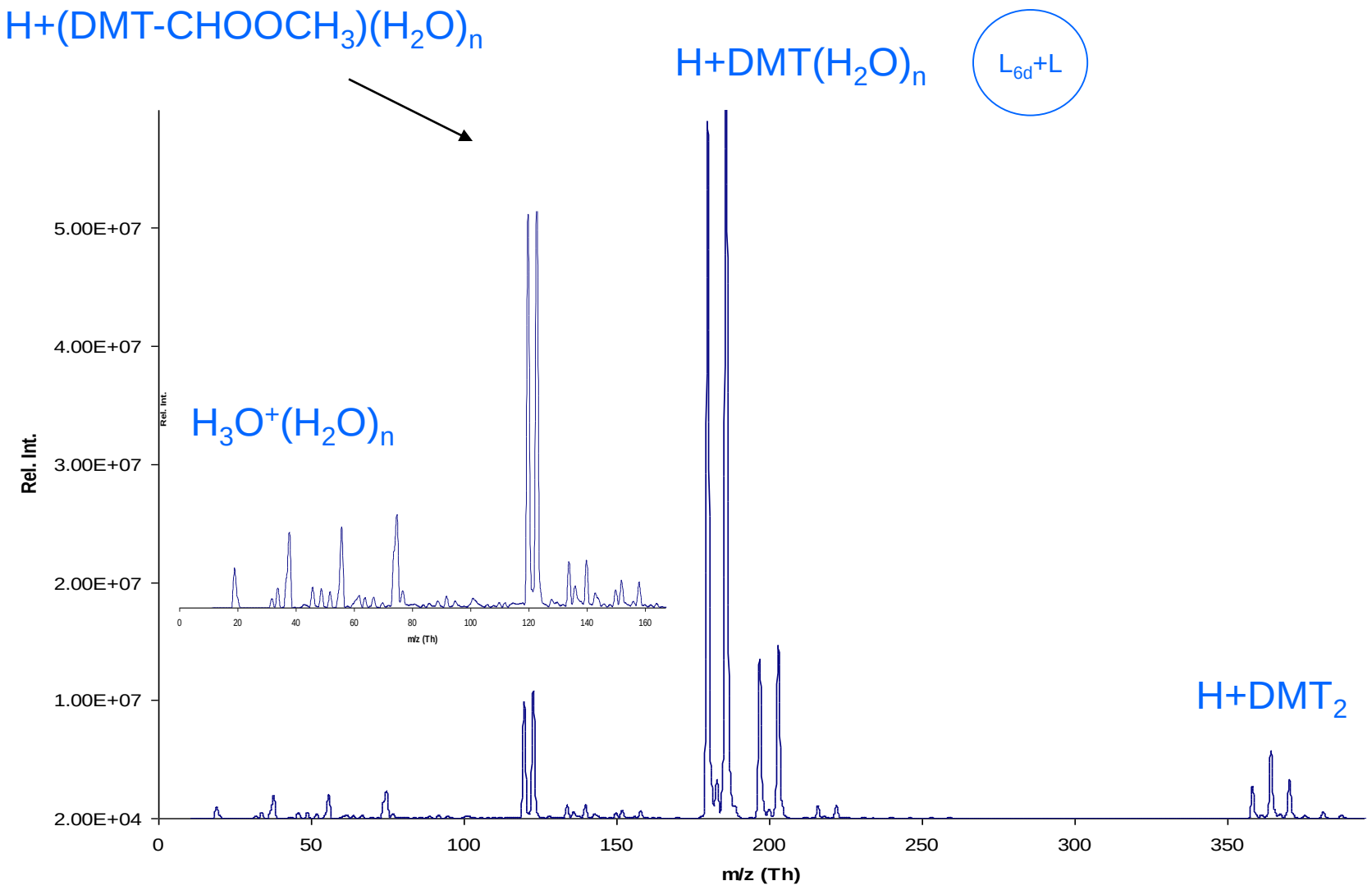

Corona region
Nanospray tip

Mass spectrum of corona ions at 40C

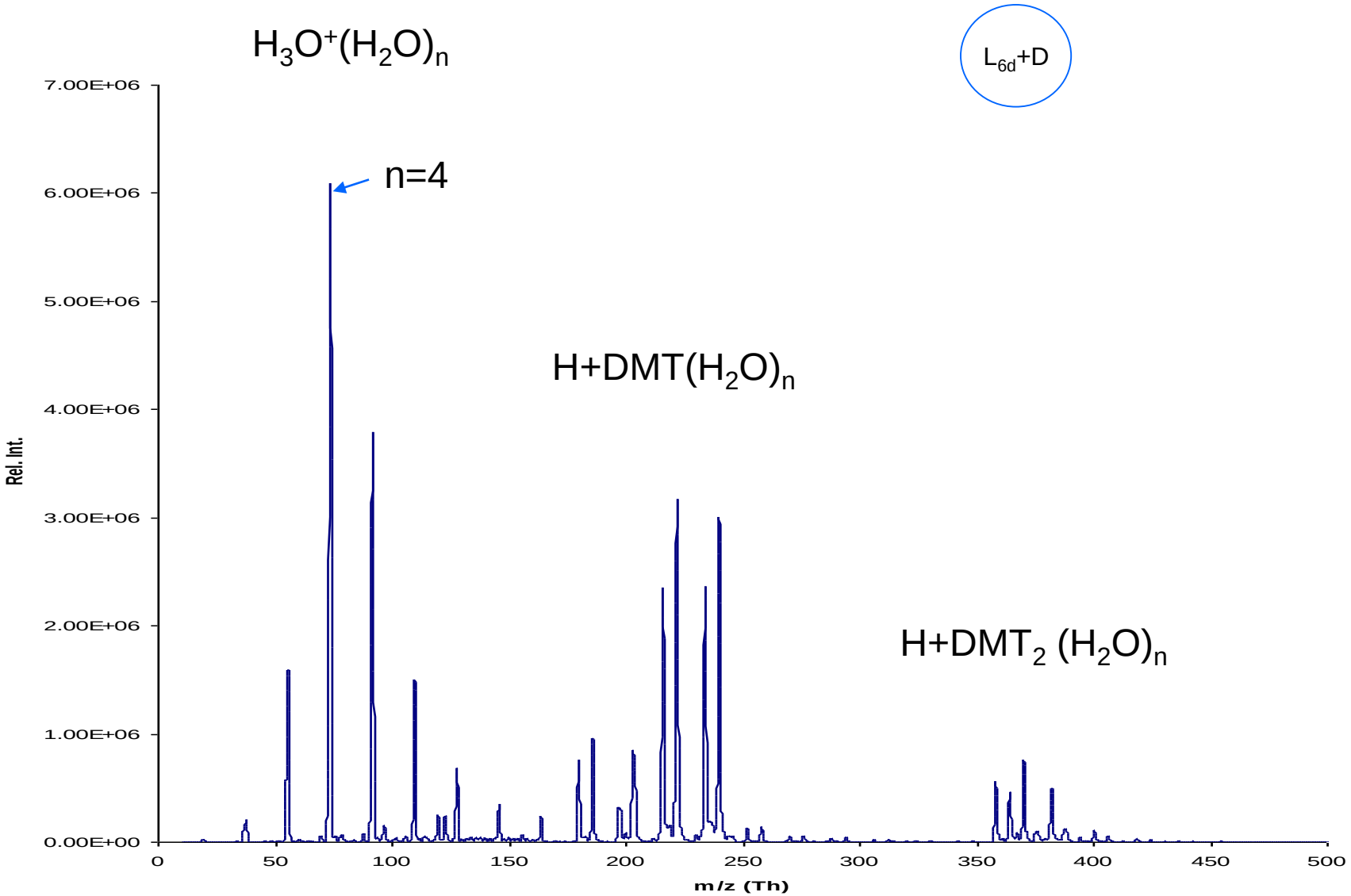



Labeled L-DMT reference sample
DMT sample of “unknown” chirality

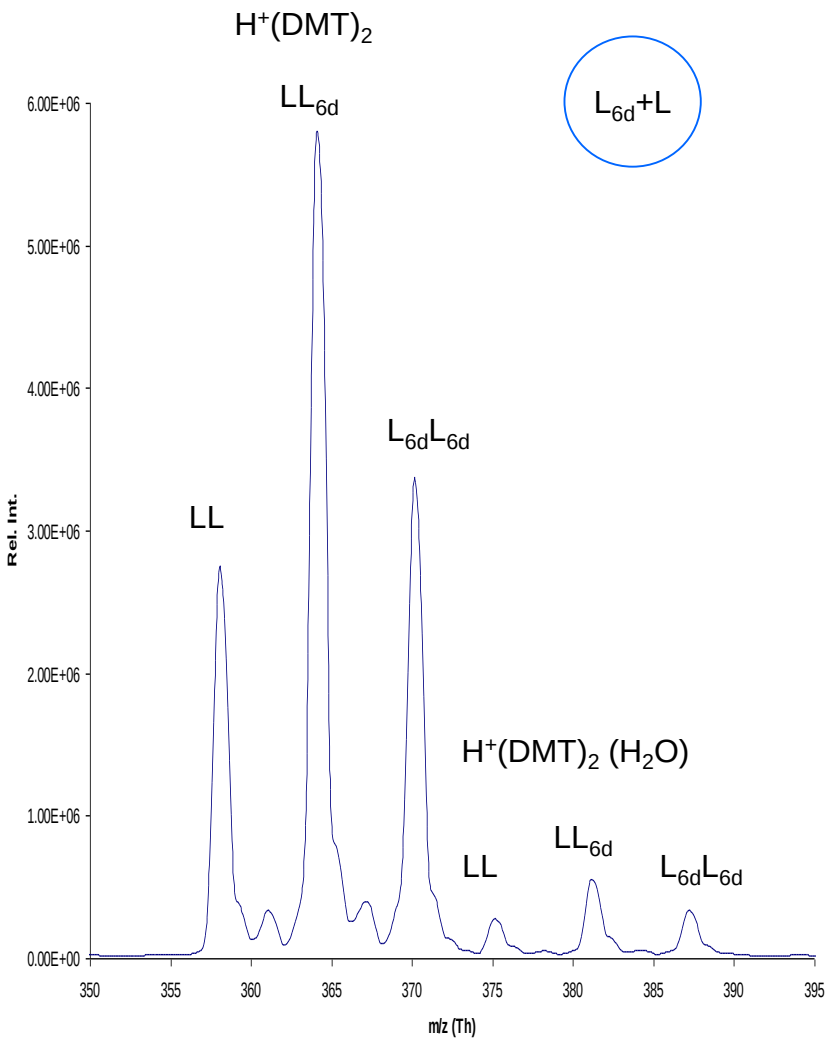
DMT vapors in laboratory air at 90C
$L + L_{6d}$

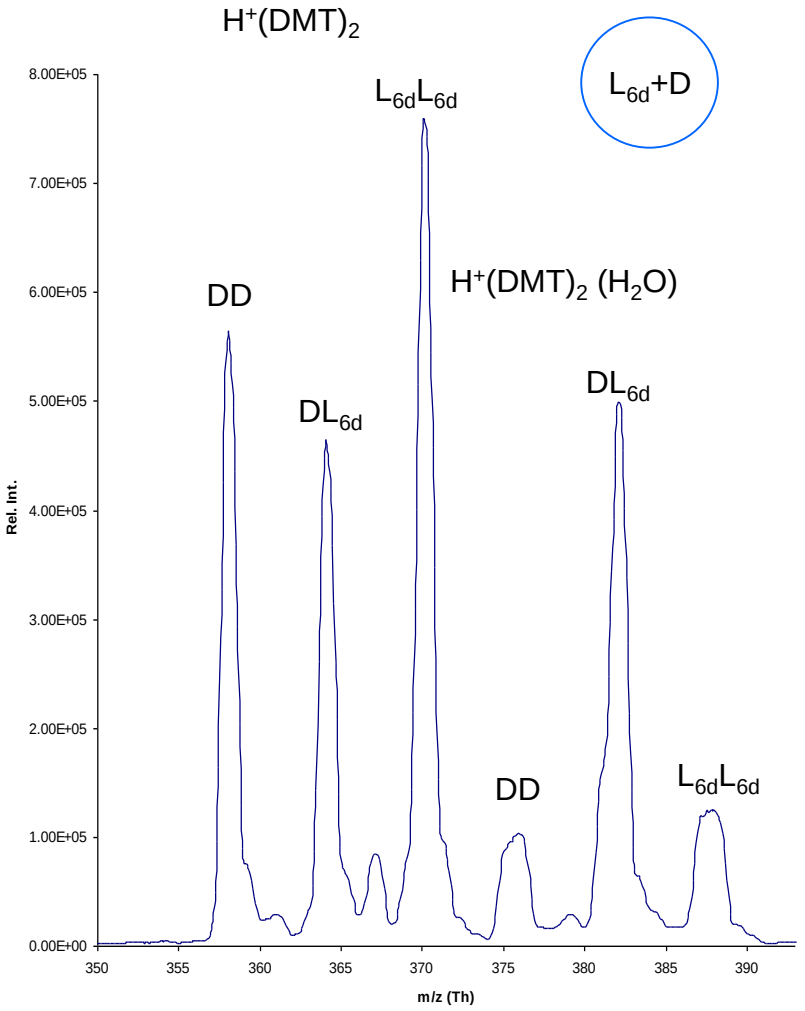


DMT vapors in laboratory air at 80C
D + L_{6d}

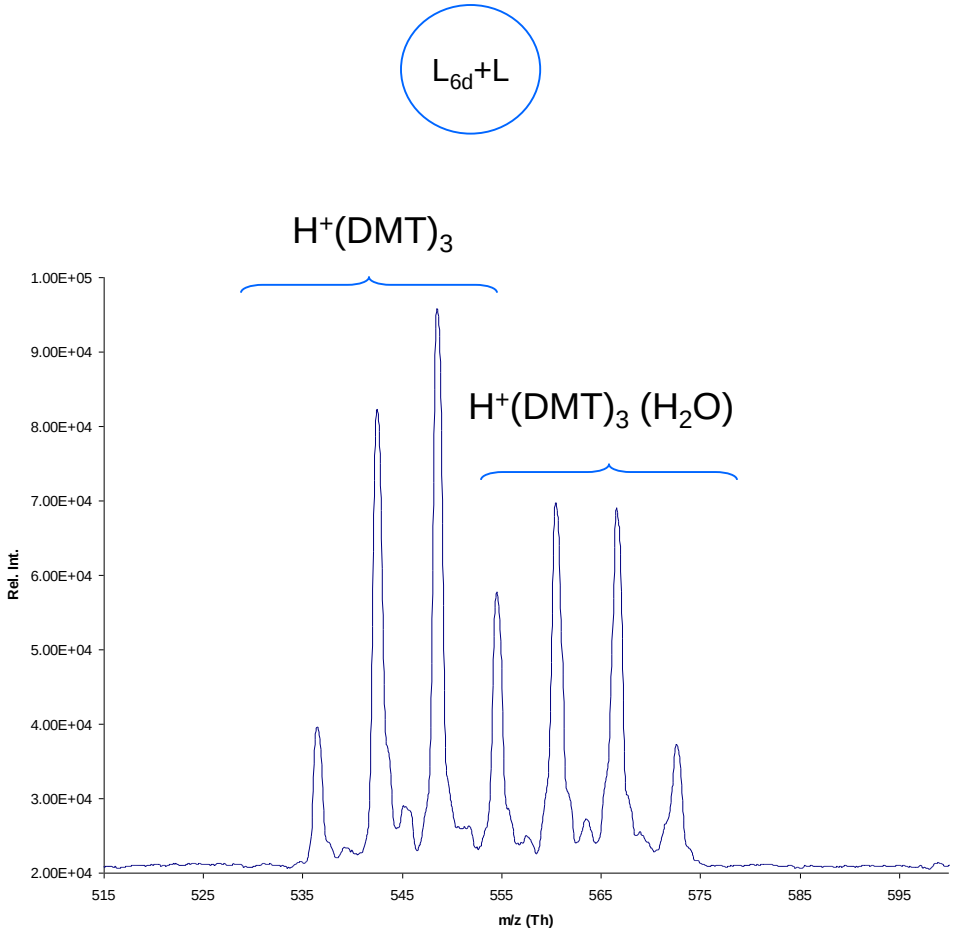


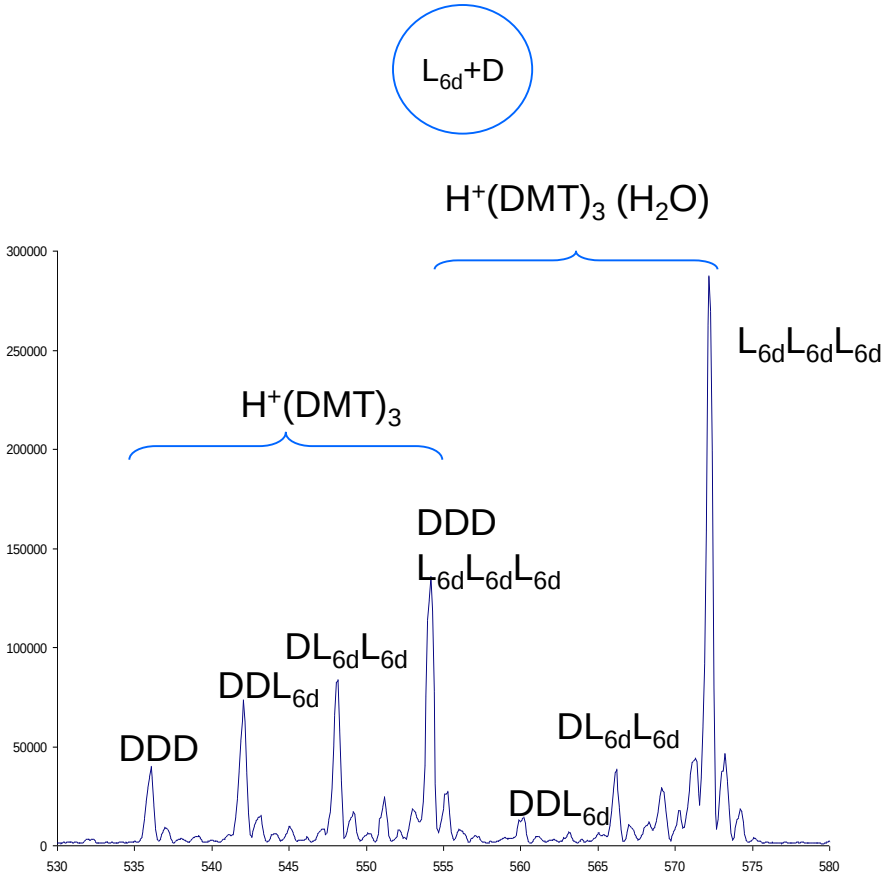
Protonated DMT dimers from molecules of the same (left) and different (right) chirality



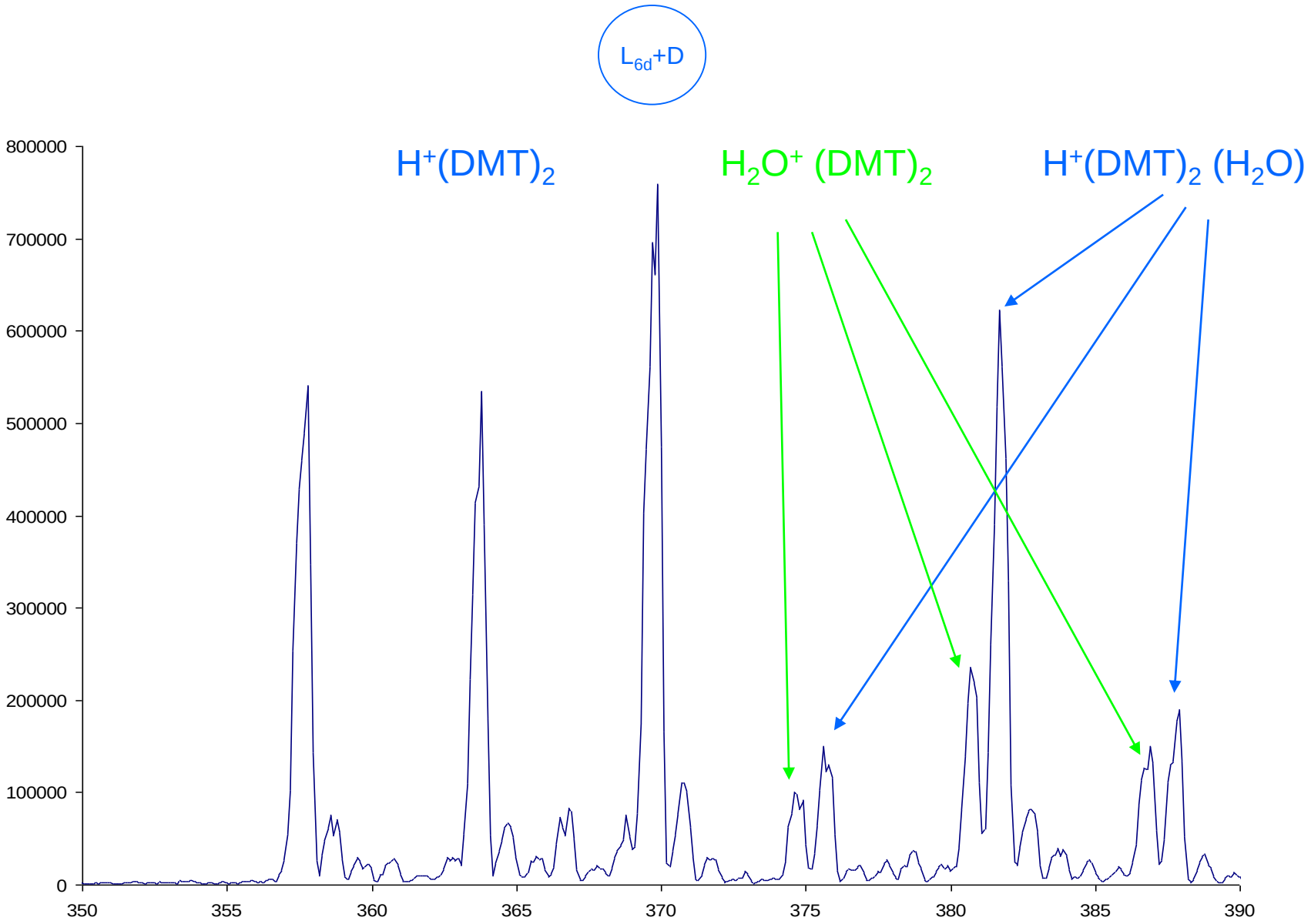


Protonated DMT trimers from molecules of different chirality

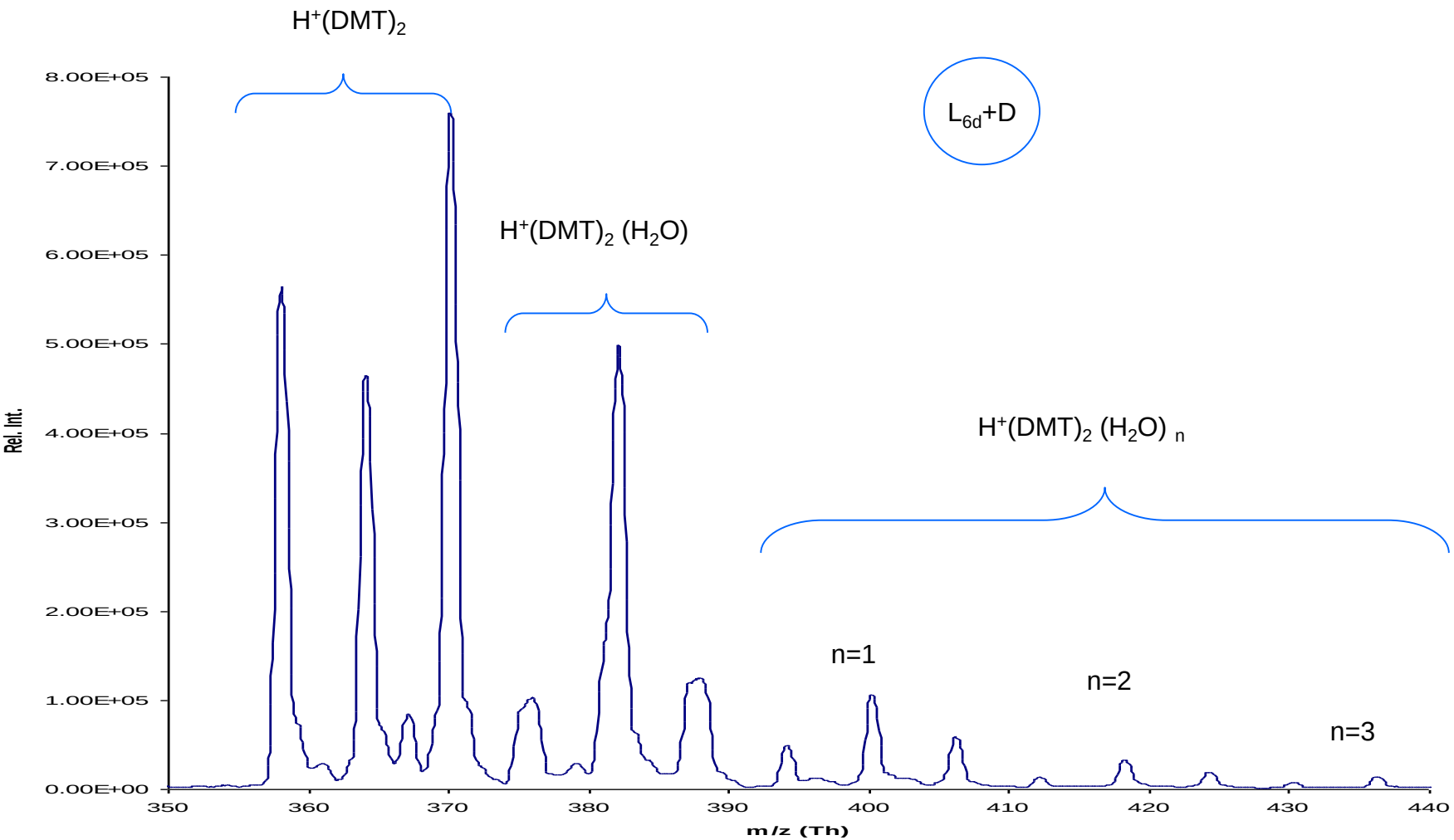




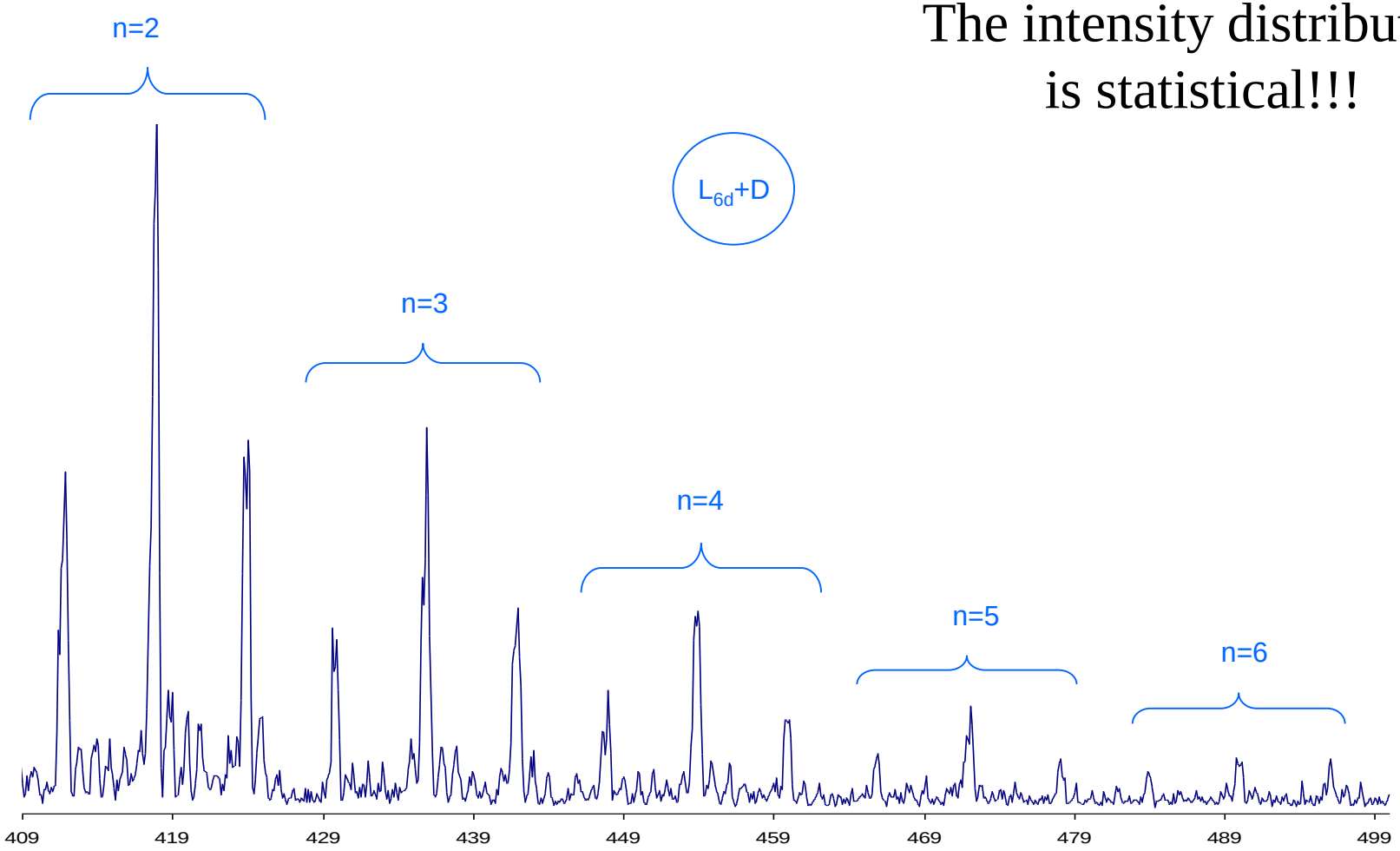
Protonated DMT dimers from molecules of different chirality L_{6d}+D



Water containing protonated dimers



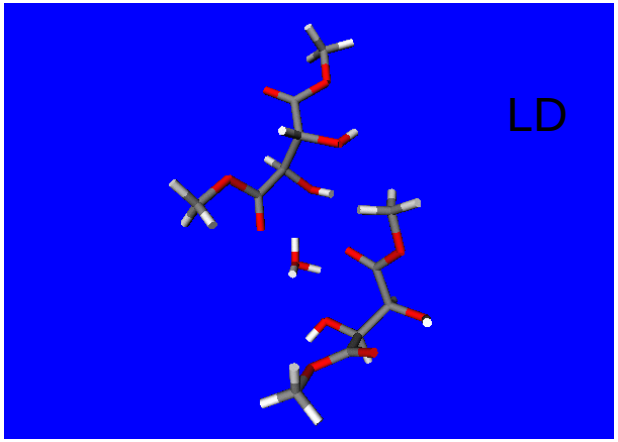
$H^+(DMT)_2\ (H_2O)_n$



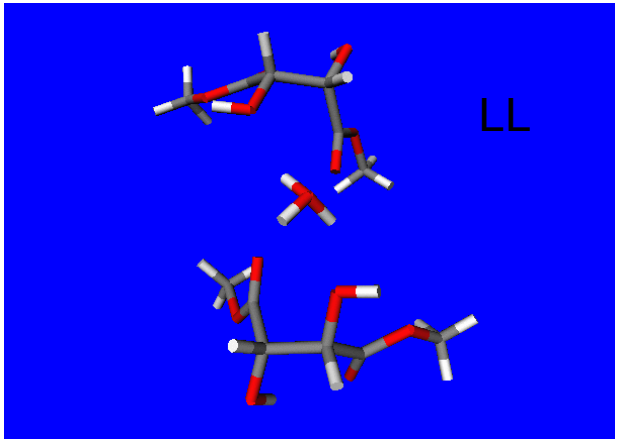
The intensity distribution is statistical!!!

$H^+(DMT)_2\ (H_2O)$ group

Ab initio Becke,Lee,Yang,Parr Method in 6-311G* bases



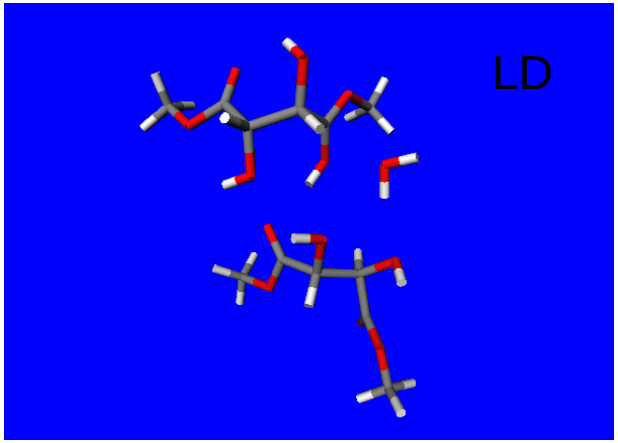
1.8kcal/mole



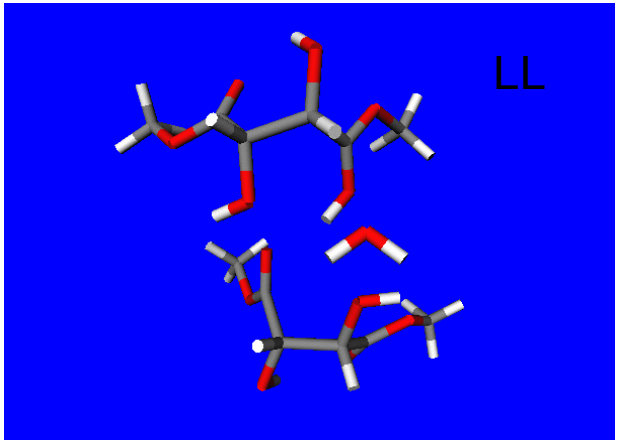
0.5 kcal/mole

ΔΔG=-2.3kcal/mole

5 kcal/mole

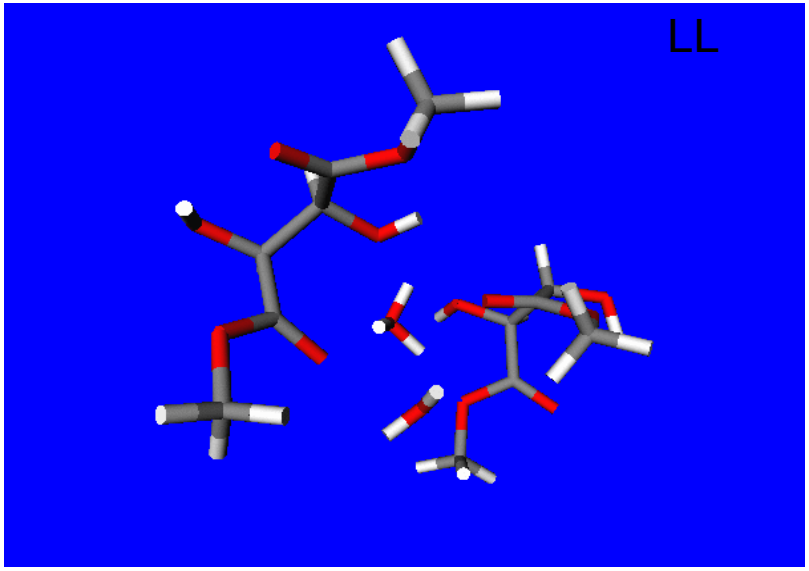


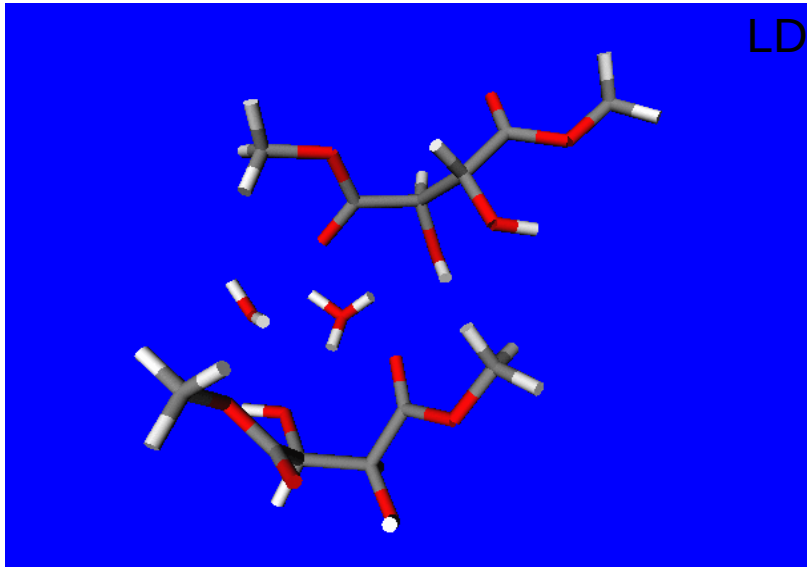
7.3kcal/mole



$H^+(DMT)_2\ (H_2O)_2$ group

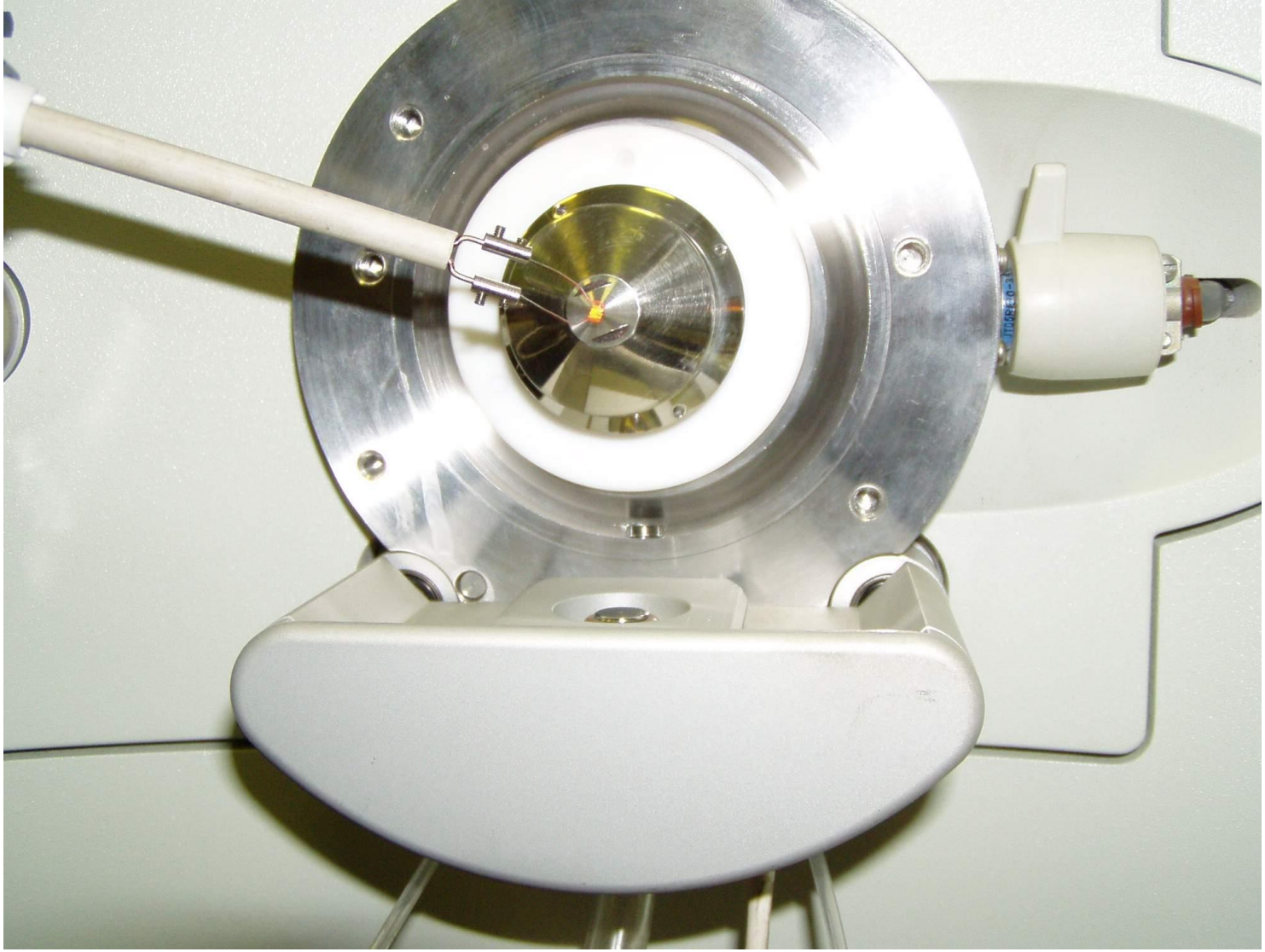
Ab initio Becke,Lee,Yang,Parr
Method in 6-311G* bases





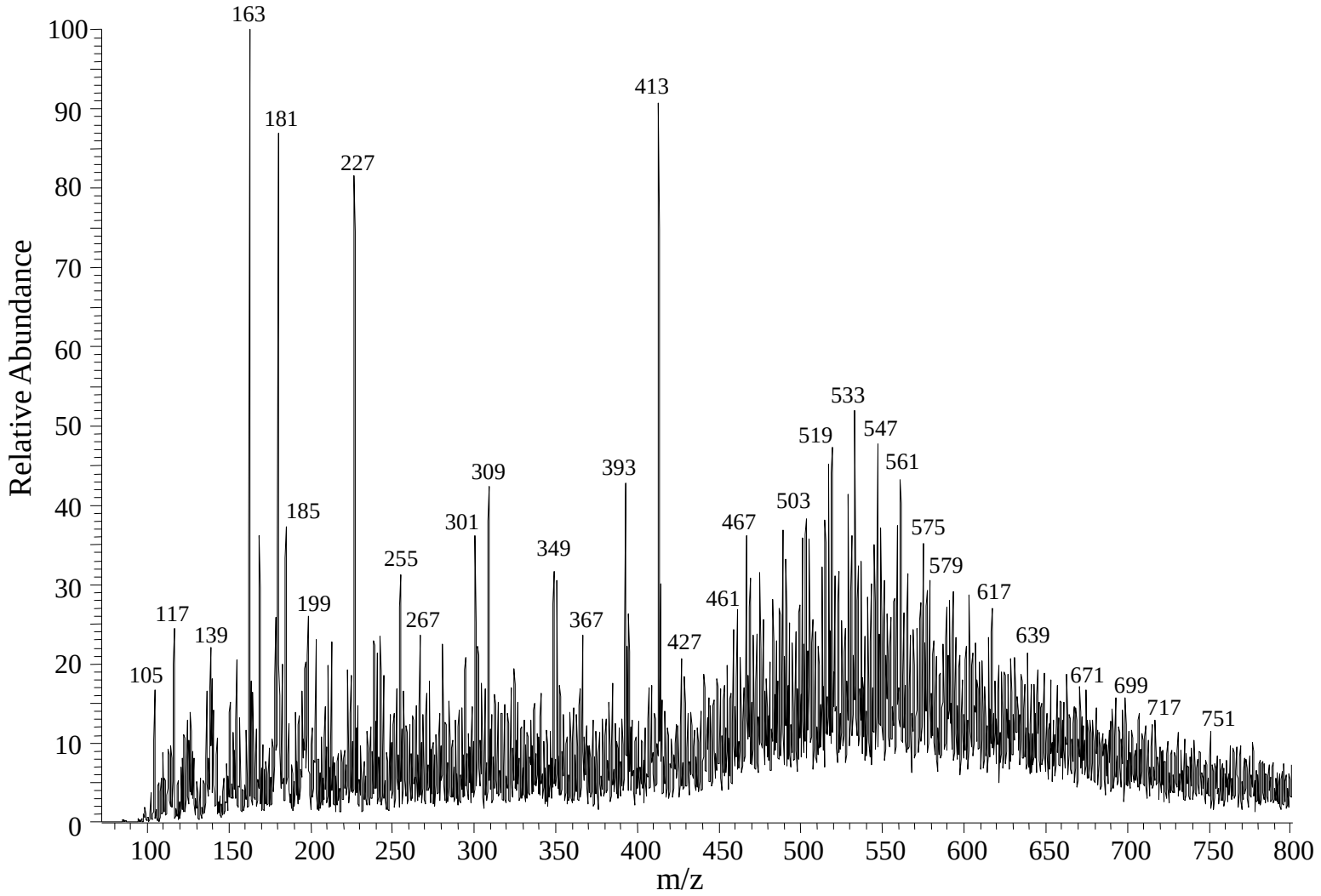
ΔΔG= 0.23 kcal/mole

Other ionization methods

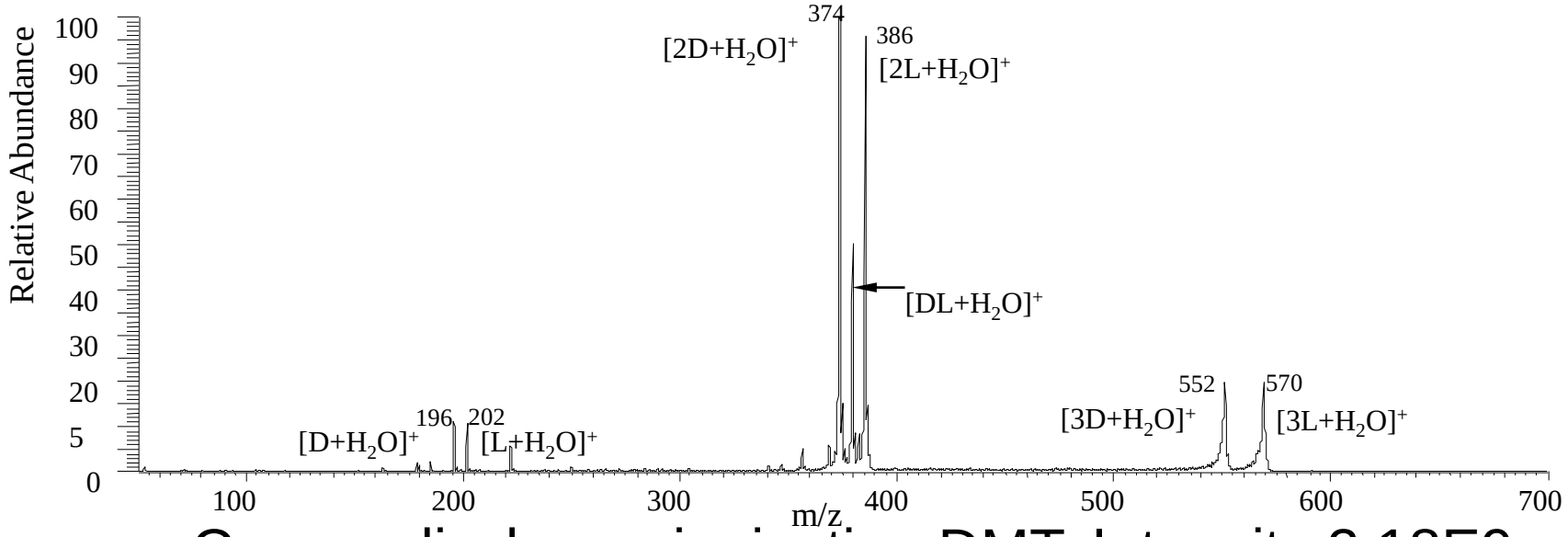


Home-built
AP thermoionization source

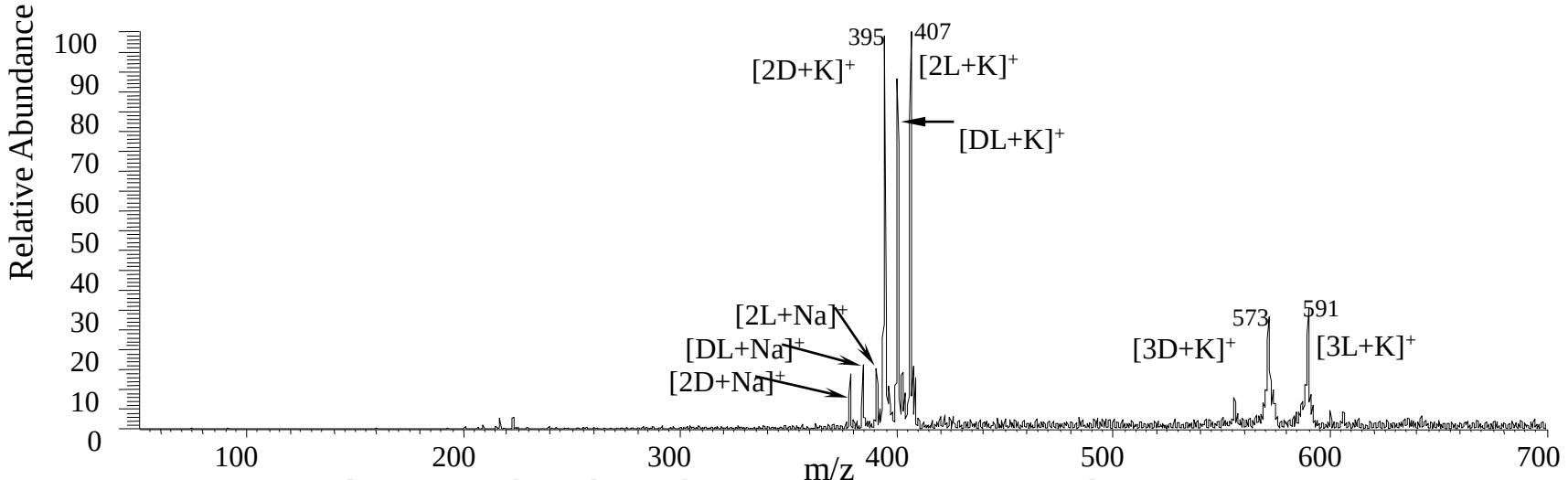
Atmospheric pressure thermoemitter



Thermoionization: Room Air



Corona discharge ionization DMT, Intensity 2.18E9



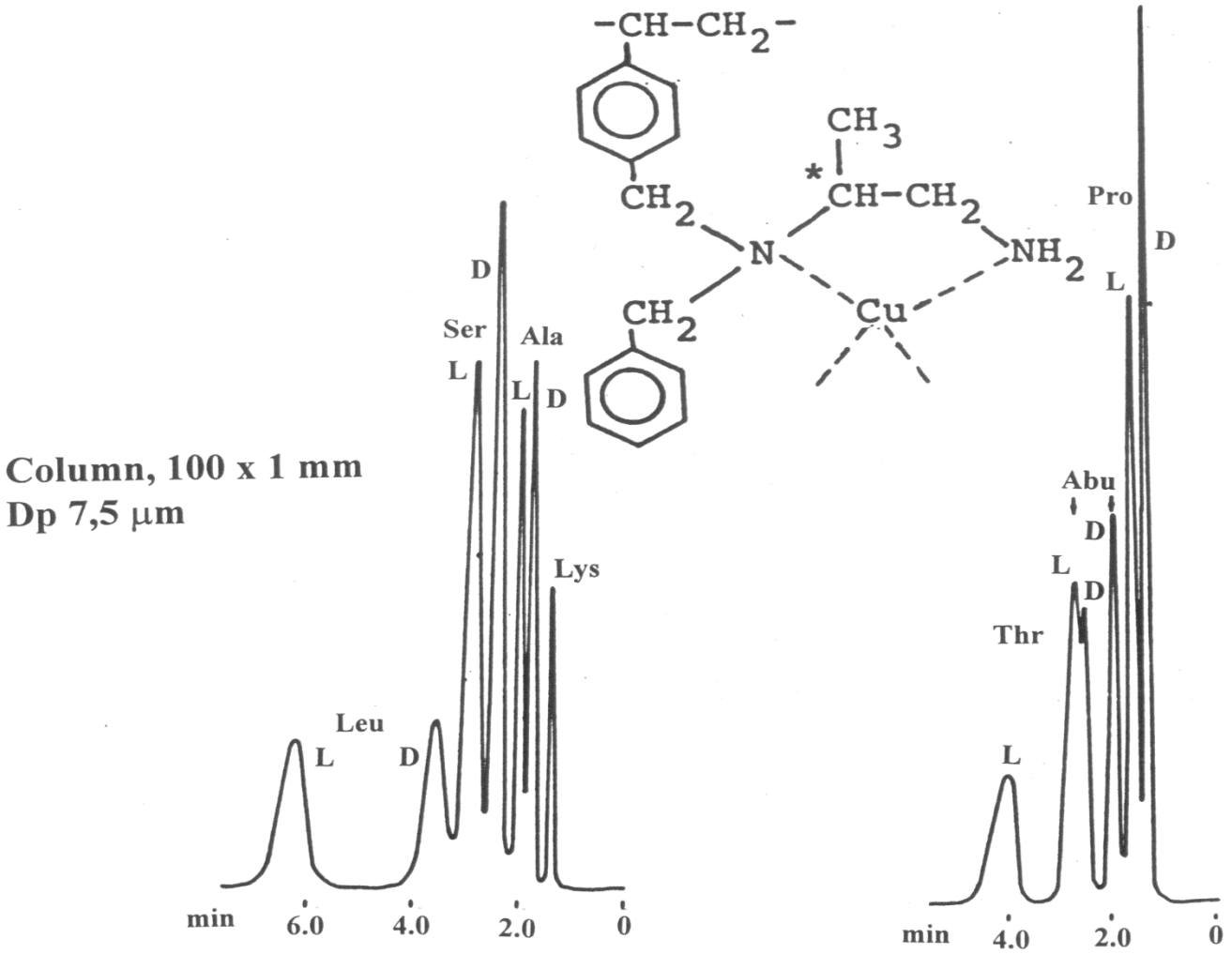
Thermoionization DMT, Intensity 1.80E8

Chiral recognition

Methods of chiral recognition currently available

- Optical (of historic interest)
- Gas chromatography(needs chemical modification of analyte)
- Capillary electrophoreses(water based phases)
- Liquid chromatography(low temperatures are possible)
- Mass spectrometry(more robust, complete identification of the sample)

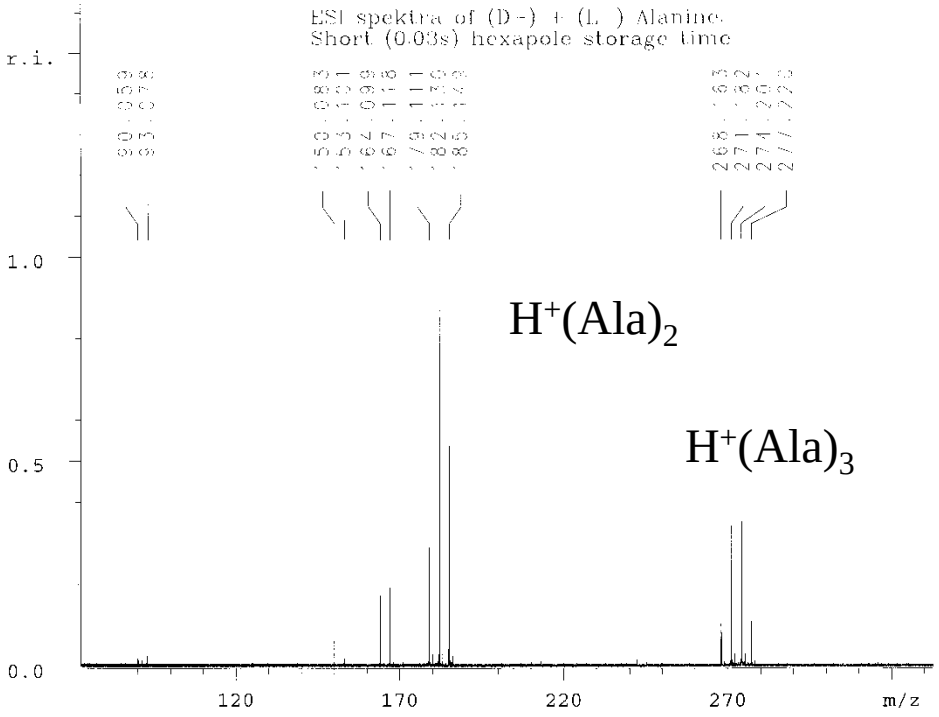
Chiral resolution of unmodified amino acid mixture by ligand-exchange liquid chromatography

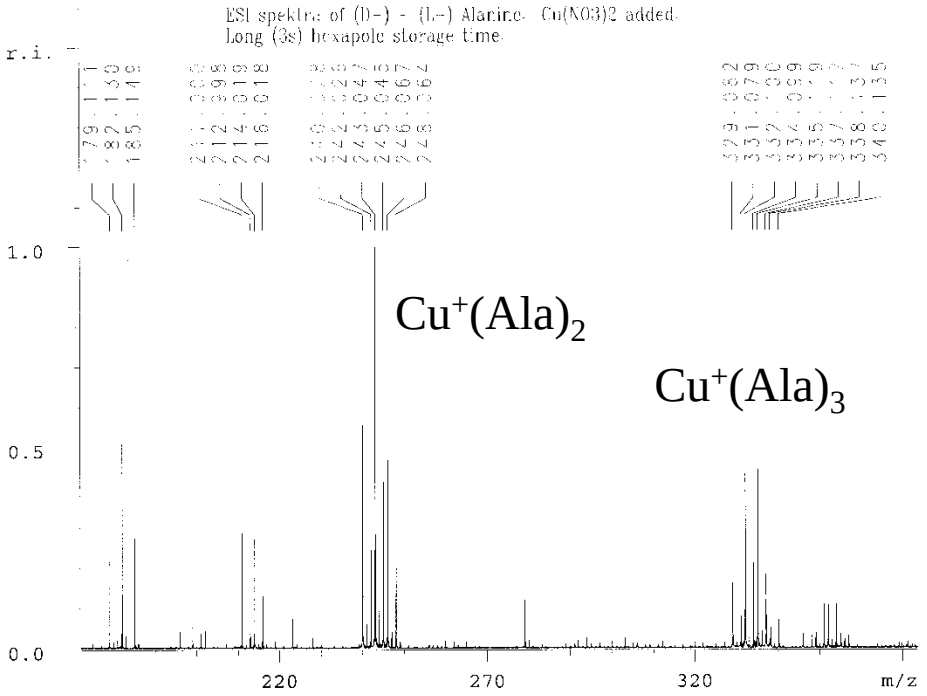


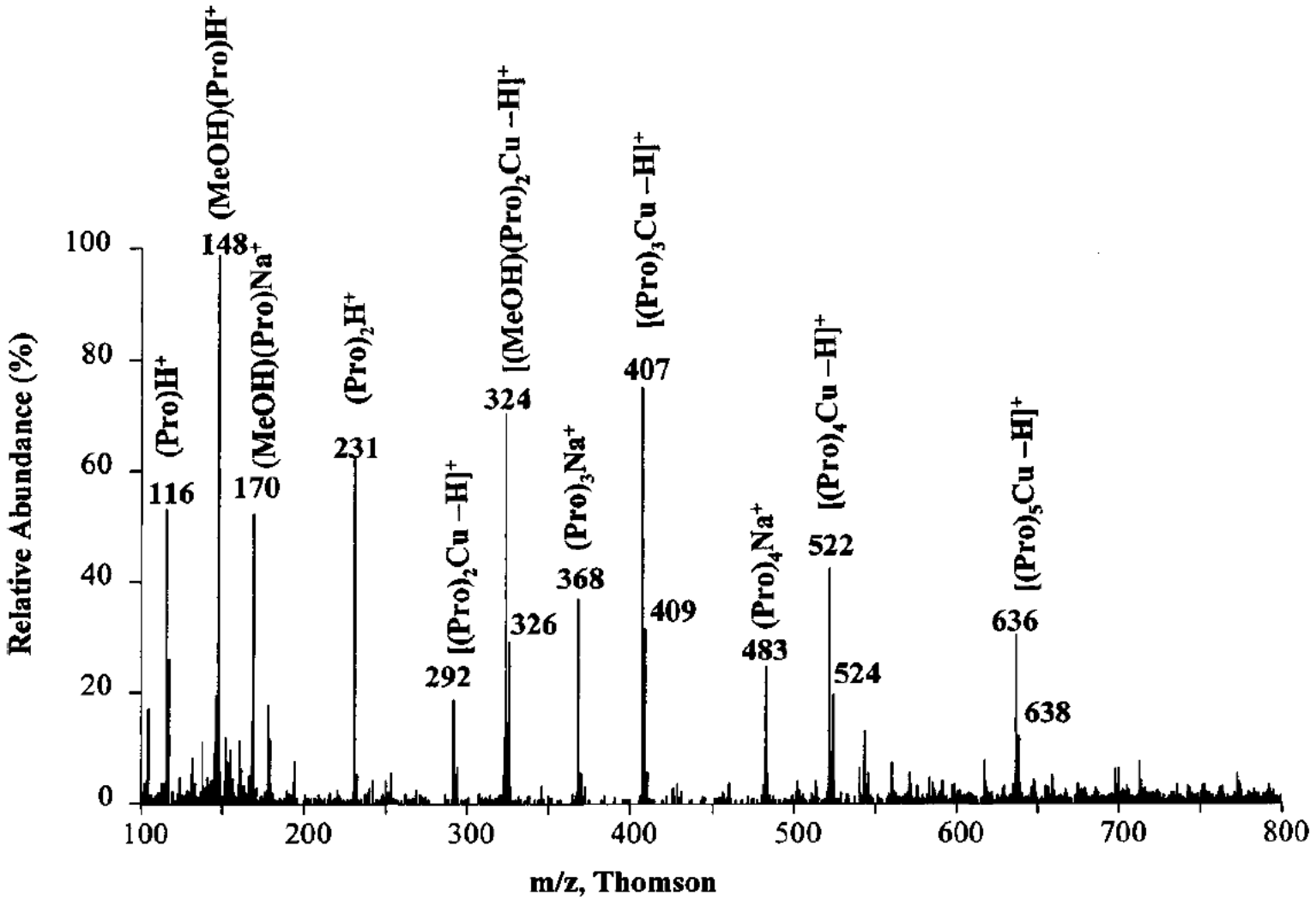
Characterization of chirality influence on ion-molecular complex stability and recognition of chirality by mass spectrometry

- Fales
- Winkler
- Nikolaev
- Sawada
- Lebrilla
- Futrell
- Hashimoto
- Okamura
- Vekey
- Tabet
- Cooks
- ...

Protonated and Cu^{++}based adducts of alanine (ESI FT ICR spectra)

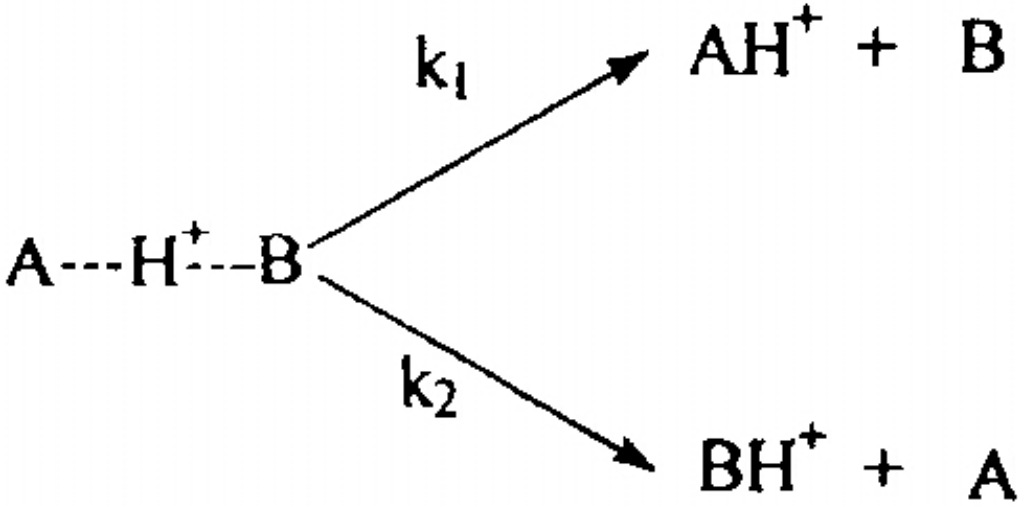






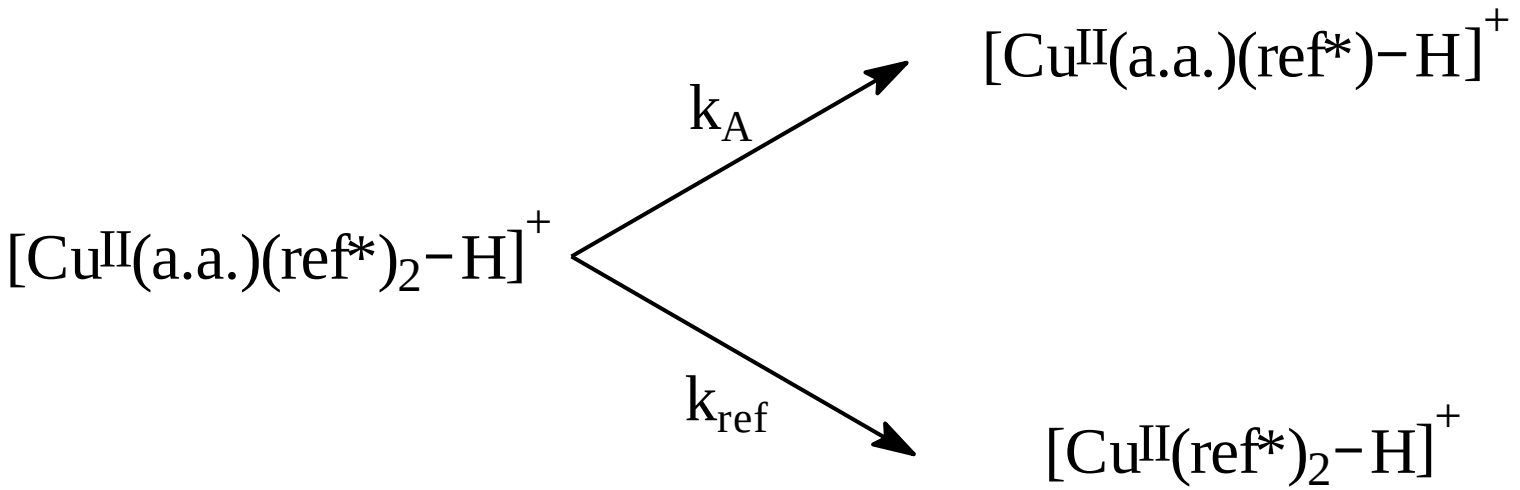
ESI mass spectrum of copper(II)-proline solution. Major cluster ions are indicated. Note the series of ions $[(Pro)_nCu^{II} - H]+$ in which n = 2-5. The spectrum was recorded for a 50:50 water:methanol solution of 10 μM proline and 2.5 μM $CuCl_2 \cdot 2H_2O$.

Kinetic method of proton affinity determination



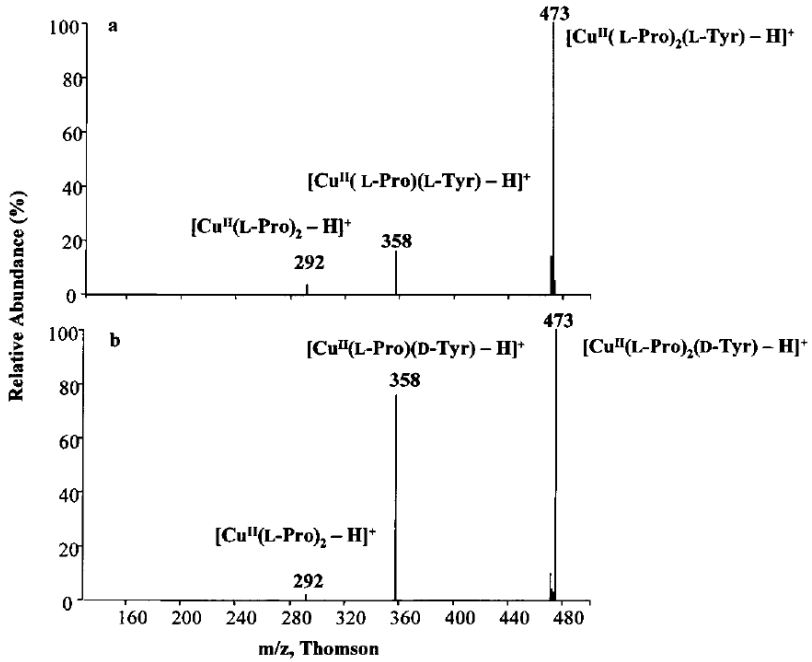
$$\ln \frac{k_1}{k_2} = \ln \frac{[\mathrm{AH}]^+}{[\mathrm{BH}]^+} = \frac{\Delta PA}{RT_{\mathrm{eff}}}$$

Kinetic method of chiral recognition



$$R = \frac{[Cu^{2+}(a.a)(ref^*) - H]^+_{hetero} / [Cu^{2+}(ref^*)_2 - H]^+}{[[Cu^{2+}(a.a)(ref^*) - H]^+_{homo} / [Cu^{2+}(ref^*)_2 - H]^+}$$

Tao, W. A.; Zhang, Duxi; Nikolaev, Eugene N.; Cooks, R. Graham., JACS (2000), 10598-10609.



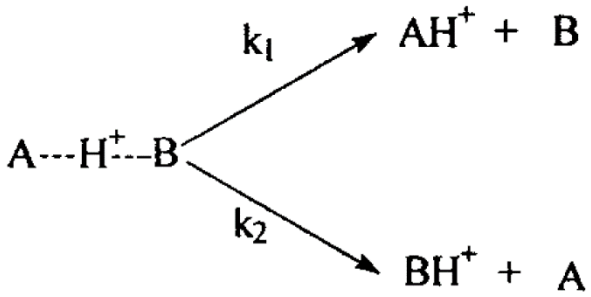


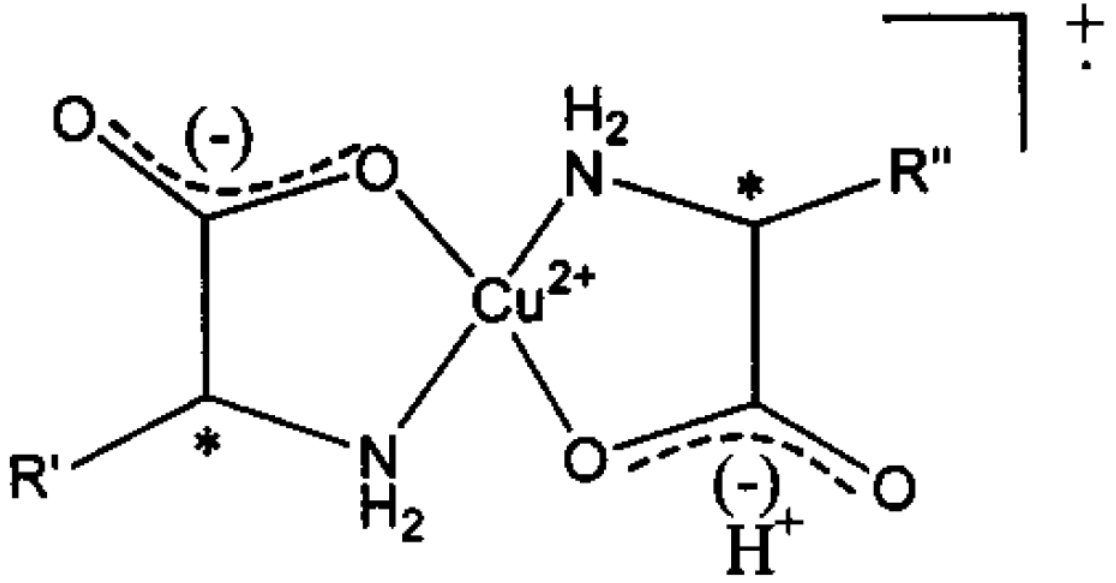
Figure 4. MS^2 product ion spectra of (a) [^{63}Cu^{II}(L-Pro)$_2$(L-Tyr) − H]$^{+\cdot}$(*m/z* 473); (b) [^{63}Cu^{II}(L-Pro)$_2$(D-Tyr) − H]$^{+\cdot}$ (*m/z* 473). CID activation level was chosen as 10%, corresponding to approximately 250 mV AC.

Table 4. Fragment Ion Abundance Ratios of [Cu^{II}(A)(ref*) − H]$^{+\cdot}$/[Cu^{II}(ref*)$_2$ -H]$^{+\cdot}$ in the MS^2 Spectra of [Cu^{II}(ref*)$_2$((a) − H]$^{+\cdot}$ at Different Relative Concentration Ratios of Analyte (A) and Chiral Reference (ref*)[a]

[ref*]/[A] in the solution	4:1	2:1	1:1	1:2	1:4
[(L-Phe)(L-Thr)Cu^{II} − H]$^{+\cdot}$/[(L-Phe)$_2$Cu^{II} − H]$^{+\cdot}$	0.77	0.77	0.76	0.78	0.75
[(L-Phe)(L-Pro)Cu^{II} − H]$^{+\cdot}$/[(L-Phe)$_2$Cu^{II} − H]$^{+\cdot}$	1.9	2.2	2.2	2.4	2.9
[(L-Pro)(L-Tyr)Cu^{II} − H]$^{+\cdot}$/[(L-Pro)$_2$Cu^{II} − H]$^{+\cdot}$	4.2	4.2	4.2	4.2	4.3
[(L-Pro)(D-Tyr)Cu^{II} − H]$^{+\cdot}$/[(L-Pro)$_2$Cu^{II} − H]$^{+\cdot}$	36	37	39	38	43
[(L-Pro)(L-Phe)Cu^{II} − H]$^{+\cdot}$/[(L-Pro)$_2$Cu^{II} − H]$^{+\cdot}$	1.8	1.8	1.9	1.9	1.9
[(L-Pro)(L-Leu)Cu^{II} − H]$^{+\cdot}$/[(L-Pro)$_2$Cu^{II} − H]$^{+\cdot}$	0.13	0.13	0.13	0.12	0.10
[(L-Pro)(L-Met)Cu^{II} − H]$^{+\cdot}$/[(L-Pro)$_2$Cu^{II} − H]$^{+\cdot}$	23	27	26	28	34
[(L-Pro)(L-Thr)Cu^{II} − H]$^{+\cdot}$/[(L-Pro)$_2$Cu^{II} − H]$^{+\cdot}$	0.87	0.89	0.87	0.88	0.85
[(L-Pro)(L-Asp)Cu^{II} − H]$^{+\cdot}$/[(L-Pro)$_2$Cu^{II} − H]$^{+\cdot}$	2.0	3.0	2.9	3.0	3.0

[a] CID activation level was chosen as 10%, corresponding to approximately 250 mV AC dipolar excitation.

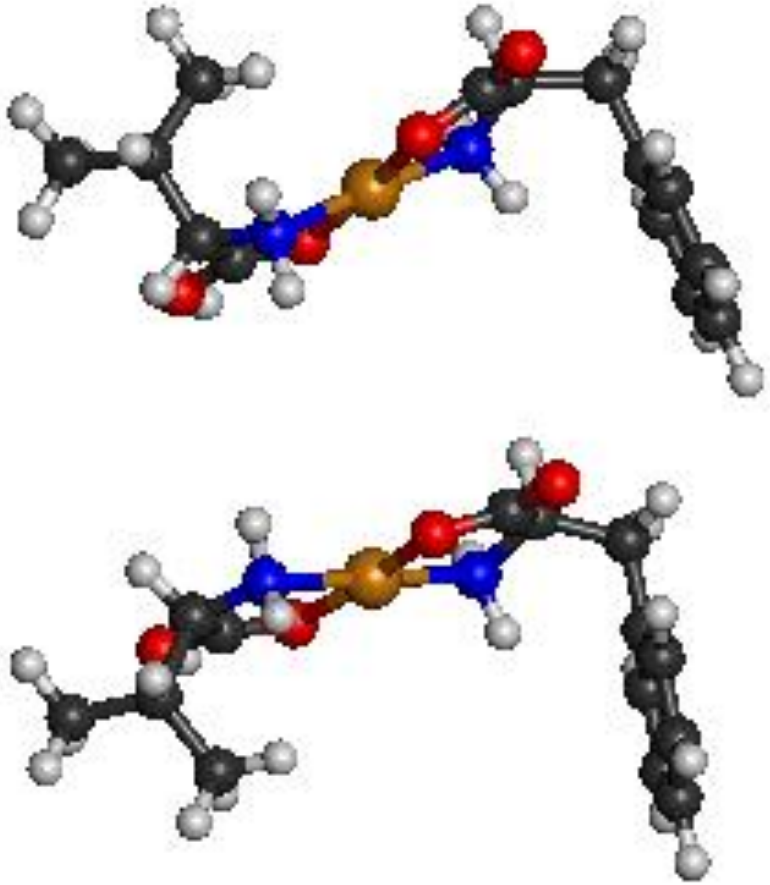
The nature of molecular chiral recognition in amino acid Cu^{II} clusters



$$[Cu^{II}(A)(ref^*)_2\text{–}H]^+ \xrightarrow{k_A} [Cu^{II}(A)(ref^*)\text{–}H]^+ + ref^*$$

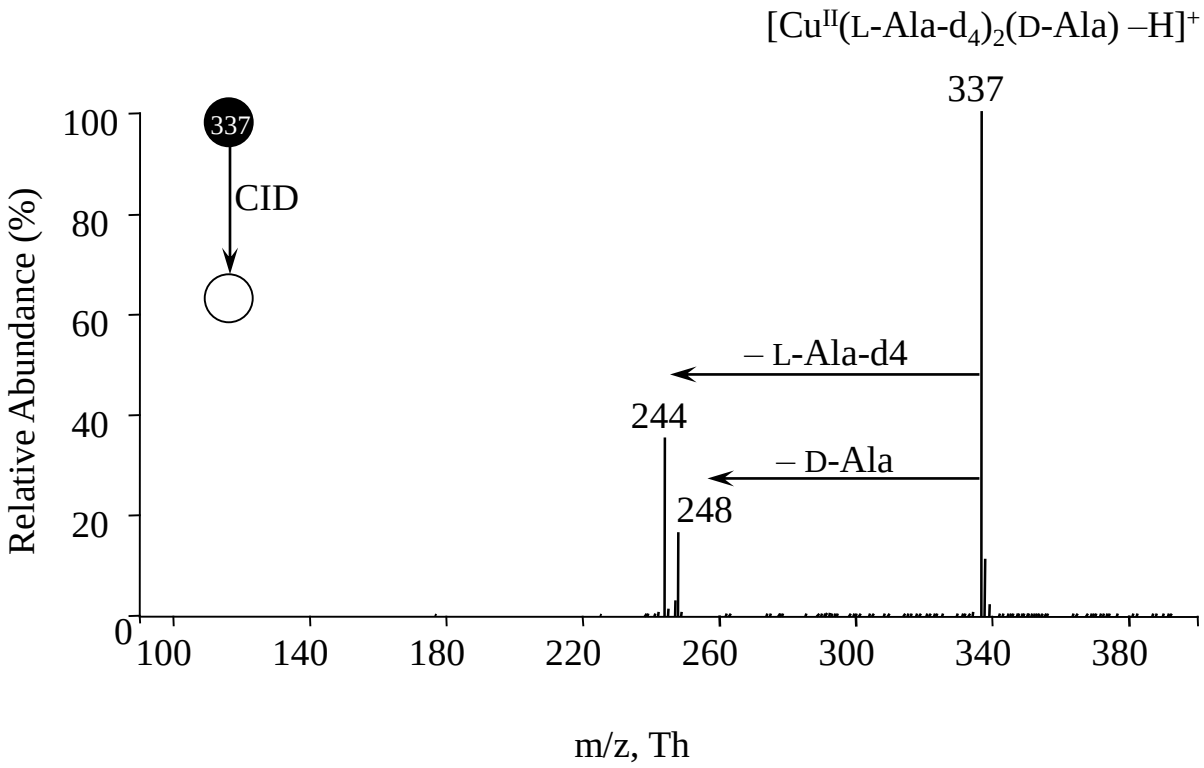
$$[Cu^{II}(A)(ref^*)_2\text{–}H]^+ \xrightarrow{k_{ref}} [Cu^{II}(ref^*)_2\text{–}H]^+ + A$$

[Cu(II) (PHE)(VAL)-H]$^{+}$

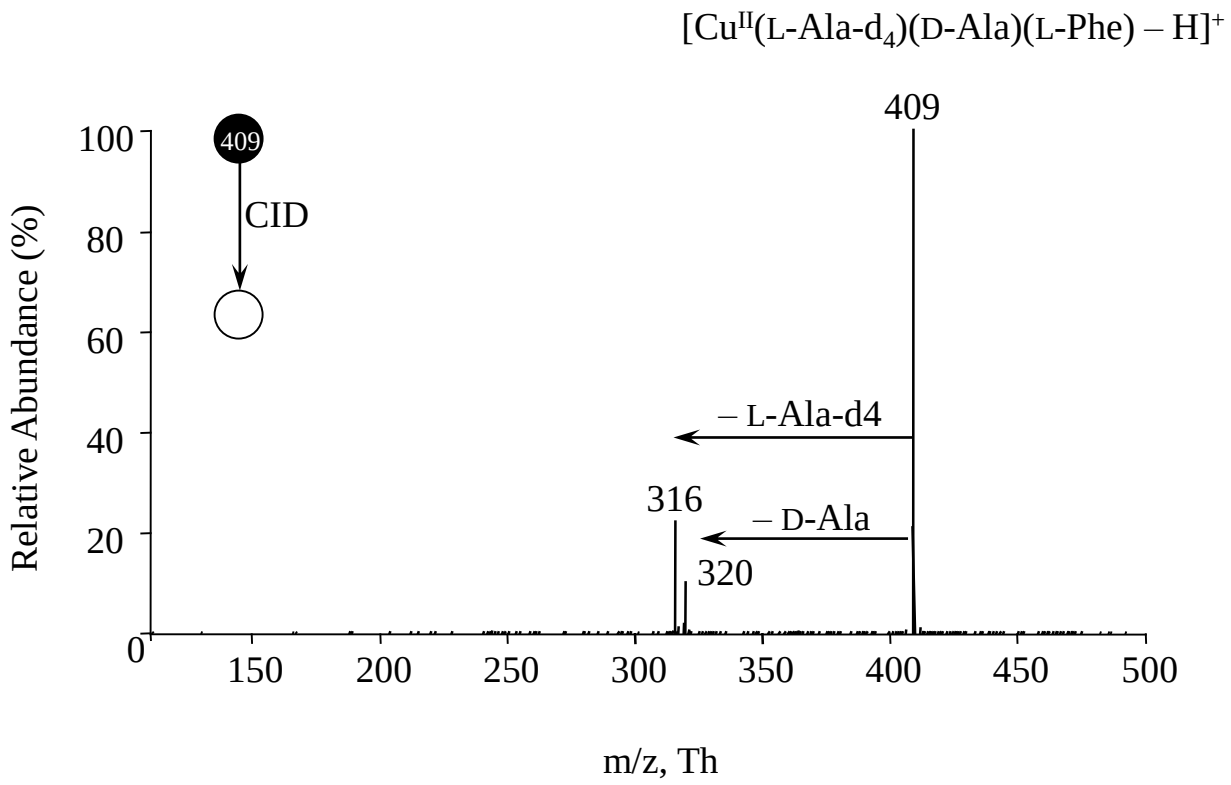


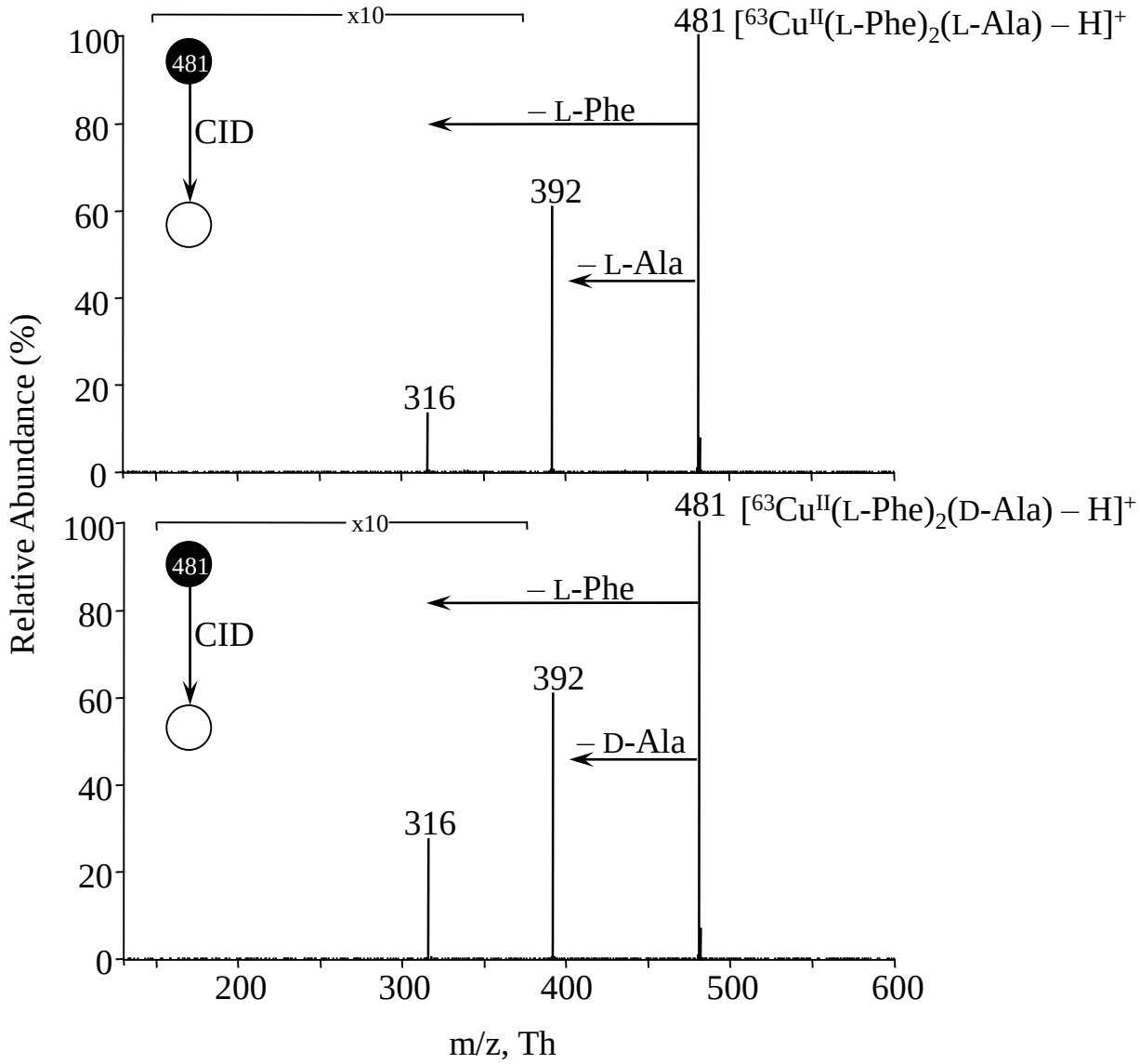
BLYP 6-311G*

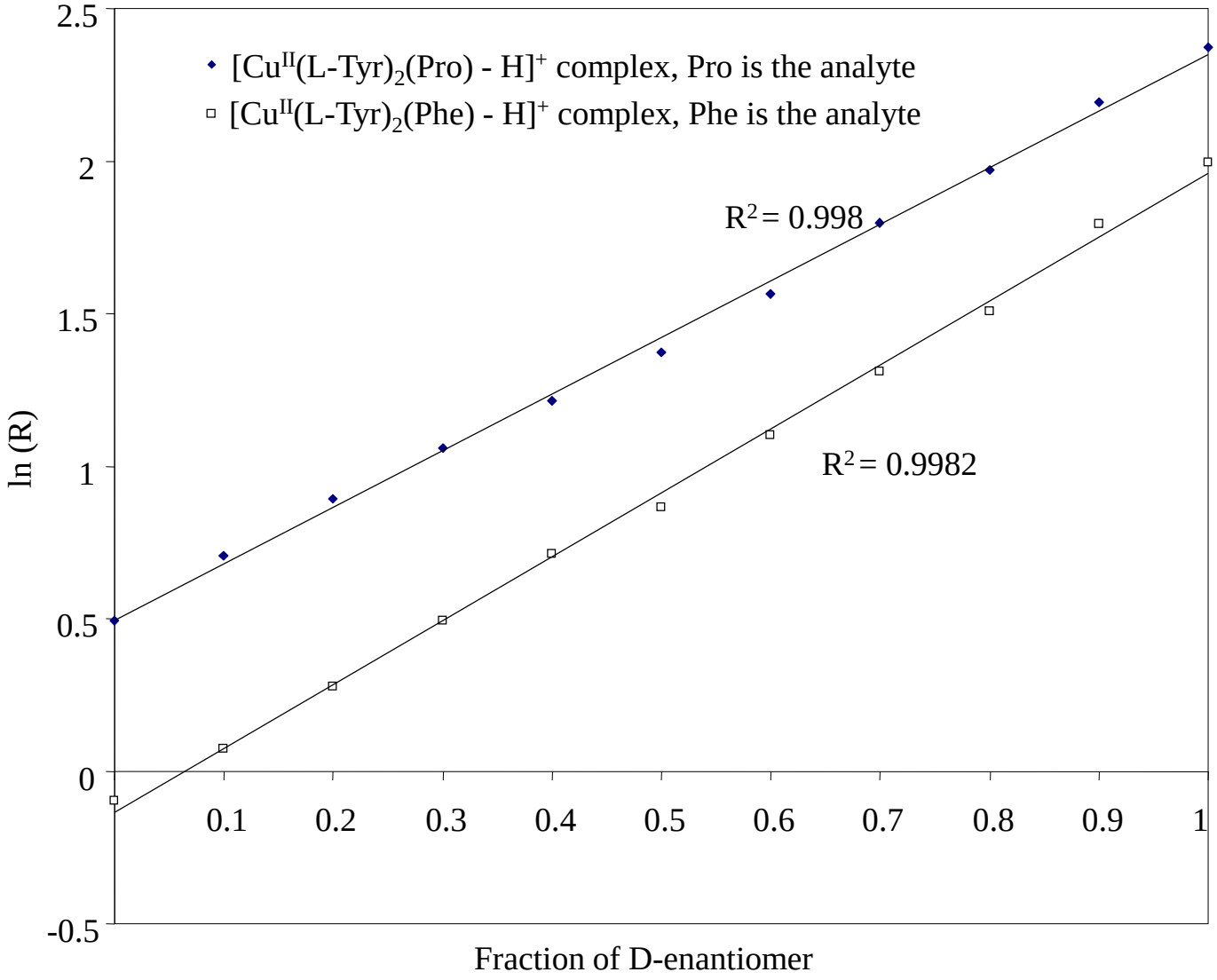
$\Delta\Delta G$ = 5.9 kJ/mol


[Cu^II(L-Ala-d4)2(D-Ala) –H]+
337
337
CID
100
80
60
40
20
0
Relative Abundance (%)
– L-Ala-d4
244
– D-Ala
248
100
140
180
220
260
300
340
380
m/z, Th

Recognition of alanine chirality by kinetic method




x10
481 [63CuII(L-Phe)2(L-Ala) – H]+
481
CID
– L-Phe
392
– L-Ala
316
x10
481 [63CuII(L-Phe)2(D-Ala) – H]+
481
CID
– L-Phe
392
– D-Ala
316
Relative Abundance (%)
m/z, Th
0
20
40
60
80
100
200
300
400
500
600



Calibration curves for chiral analysis amino acids using single ratio method with the $[Cu^{II}(A)(ref^*)_2 - H]^+$ system (A = analyte amino acid presents as a chiral mixture and ref* is the chiral reference).

Degree of Chiral Recognition of Natural Chiral α-Amino Acids[a,b]

A[a]	ref*	$[Cu^{II}(ref^*)(A) - H]^{+\cdot}/[Cu^{II}(ref^*)_2 - H]^{+\cdot}$ D-isomer	$[Cu^{II}(ref^*)(A) - H]^{+\cdot}/[Cu^{II}(ref^*)_2 - H]^{+\cdot}$ L-isomer	R_{chiral}	$\Delta(\Delta Cu^{II}BDE)$[c] (kJ/mol)
Ala	L-Phe	0.049	0.024	2.0	2.1
Val		0.75	0.17	4.5	4.3
Leu		0.96	0.41	2.3	2.5
Ile		1.7	0.36	4.8	4.6
Pro		12	2.2	5.3	4.9
Asp		3.0	1.1	2.7	2.9
Glu		11	3.7	3.1	3.3
Ser		0.28	0.18	1.5	1.2
Thr		1.4	0.76	1.8	1.7
Cys[d]					
Met	L-Trp	1.8	0.23	7.6	5.9
Phe		0.11	0.013	8.3	6.2
Tyr		0.21	0.019	11	6.9
Asn		6.1	3.3	1.8	1.7
Gln		50	7.3	6.8	5.6
Trp	L-Asn	6.1	3.3	1.8	1.7
His	L-Arg	0.022	0.046	0.47	−2.2
Lys	L-His	0.91	1.6	0.56	−1.7

[a] A = analyte amino acid. [b] CID activation level was chosen as 10%, approximately 250 mV AC dipolar excitation. [c] $\Delta(\Delta Cu^{II}BDE)$ as defined in eq 10. [d] Cysteine is oxidized to cystine.

Conclusions

• Among methods available now for chiral analyses the most fast, sensitive and informative is a mass spectrometry
• Mass spectrometry permits to reveal the mechanism of chiral discrimination/recognition
• Search for more effective chiral reference substances should be continued
•Water molecules attachment to chiral molecule complexes can promote, invert or suppress chiral discrimination.
•DFM *ab initio* calculation results are in complete agreement with observations
•Corona API and thermo API are suitable for in situ direct MS chiral recognition for relatively volatile substances