841. Heraeus-Seminar on Quantum Technologies, Sept. 1-4, 2025

The history of the Nuclear Magnetic Resonance from a (organic) chemist's perspective

Horst Kessler TU München

Institute for Advanced Study (IAS)

Bayerisches NMR-Zentrum (BNMRZ)

The History of NMR: precursors*

Arnold Sommerfeld (Theoretical Physics, LMU Munich: Quantization of angular momenta allows only distinct orientation in the magnetic field. 84 nominations to the Nobel Prize !

directional quantization

Wolfgang Pauli (student of Sommerfeld, later in Hamburg) explained satelits in spectra by nuclear spin

Exclusion principle „Pauli Principle“

Otto Stern (studied with Sommerfeld) and Walter Gerlach (Frankfurt, Sommerfeld supported Gerlach for the position in Munich). First experimental confirmation of quantization of nuclear spins (however, it was the spin of the electron, not the nuclear spin!) via molecular beam of Ag atoms in an inhomogeneour magnetic field. [1924]. Stern was nominated 82 times, Gerlach 31 times for the Nobel Prize.

Experimental proof

Isidor Isaak Rabi (and C.J. Gorter, who suggested the experiment for resonance according to the Larmor frequency $\omega=\gamma B_0$) was successful to demonstrate the resonance phenomenon.

Transitions possible

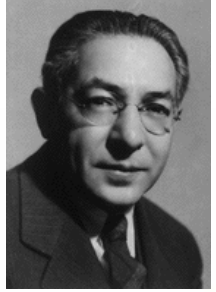
* E.D. Becker, C.L. Fisk and C.L. Khetrapal, The Development of NMR in Encyclopedia of NMR (Eds. D.M: Grant and R.K. Harris, Vol. 1, 1-158 (1996).

Walter Gerlach

Göttingen, Frankfurt, Tübingen, München

Otto Stern

Breslau, Zürich-Frankfurt, Hamburg, Pittsburgh

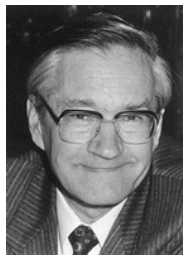


Isidor Rabi

(Hamburg, Columbia, MIT)

Wolfgang Pauli

Ph.D.Sommerfeld Munich, later Hamburg, and ETH

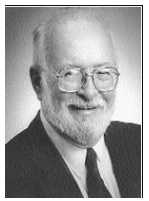


Richard Ernst

ETH Zürich

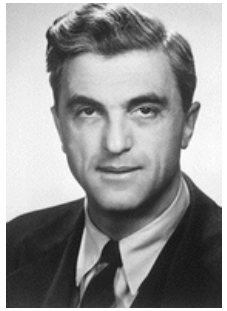
Kurt Wüthrich

ETH Zürich



Paul Lauterbur

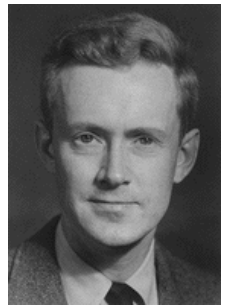
Peter Mansfield



Felix Bloch

Zürich-Leipzig-Stanford-Zürich

Ph.D. Heisenberg



Ed Purcell

Harvard

Werner Heisenberg

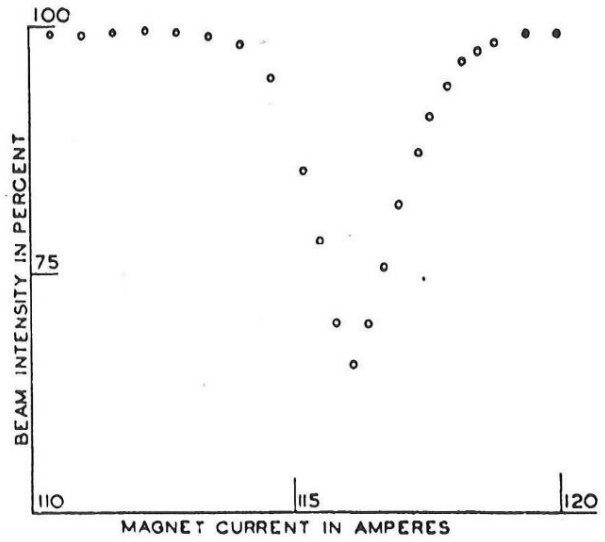
München, Göttingen, Leipzig, Göttingen, München

„small world“

during my study in Leipzig (1958-61) I did not learn anything about NMR! However, at that time almost all basic experiments were done (except 2D [1972/75 and imaging [1973])

Arnold Sommerfeld

LMU Munich -> Pauli, Rabi, Heisenberg,
81x nominated for the Nobel Prize



I.I. Rabi, J.R. Zacharias, S. Millman, P. Kusch, *Phys.Rev.* **1938**, *53*, 318.

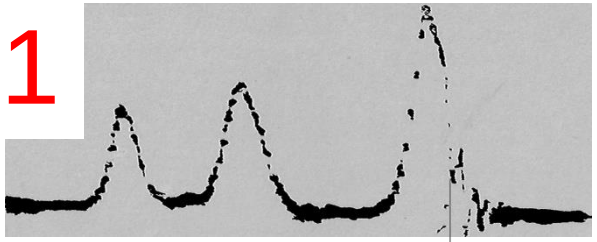
NMR in condenced phase (^{1}H-NMR)

E.M. Purcell, H.C.Torrey, R.V.Pound, *Phys. Rev.* **1946**, *69*, 37 at MIT
F. Bloch, W.W. Hansen, M. Packard, *Phys. Rev*. **1946**, *69*, 127 at Harvard

Chemical Shift (which is characteristic for chemical structure)

W.G. Proctor, F.C. Yu, *Phys. Rev*. **1950**, *77*, 717. NH_4NO_3 (^{14}N)
J.T. Arnold, S.S. Dharmatti, M.E. Packard, J.*Chem.Phys*. **1951**, *19*, 507.

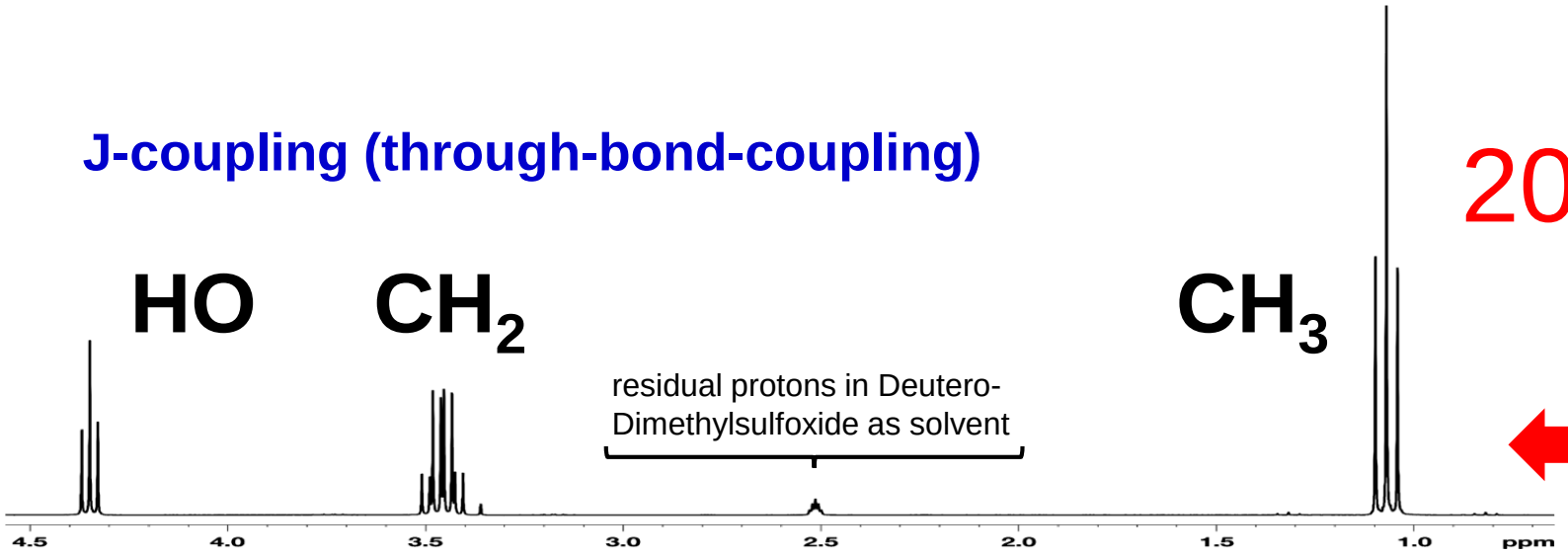
1951

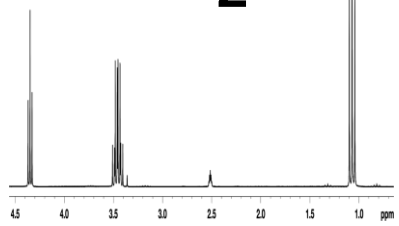


J-coupling (through-bond-coupling)

2000

HO-CH_2-CH_3





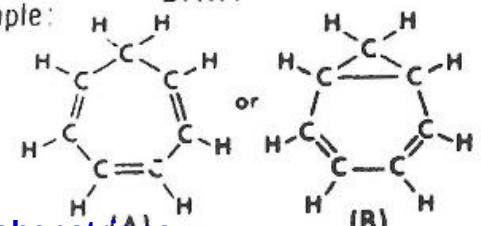
One of the first proof of chemical structure by ^{1}H NMR

[H. Kessler, Diploma Thesis **1963**, University Tübingen]

E.J.Corey, H.J. Burke, W.A.Remers, *JACS* **1955**, *77*, 4941

20 USE OF INTEGRATED INTENSITIES IN STRUCTURE ANALYSIS
(Number 20 of a series)

DATA

Sample: 

(A) or (B)

Cyclohepatriene

Volume: 0.01 cc.
Signals Observed: H^1
Frequency: 30 mc.
Field: 7050 gauss

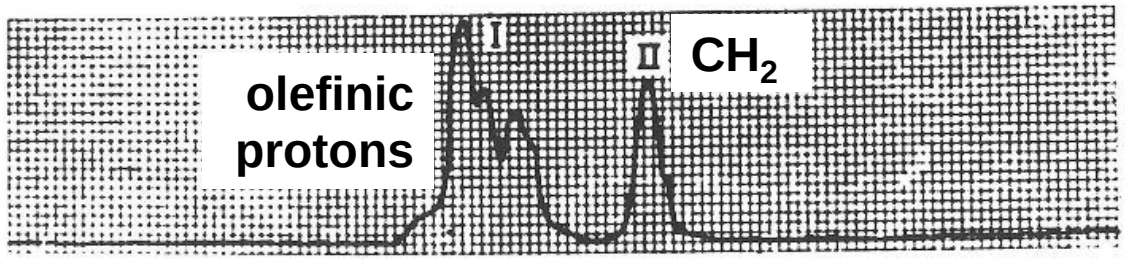
Norcaradiene

INTERPRETATION

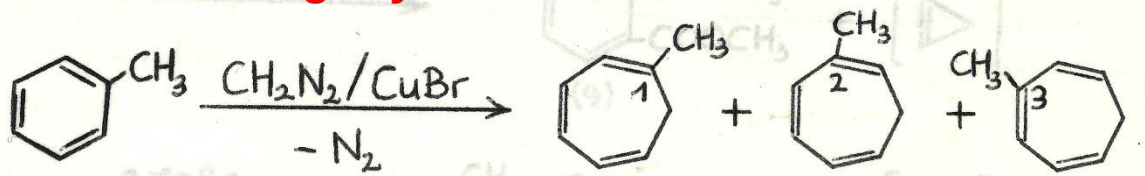
In solving the problem of whether structure A or B correctly represents the sample submitted for analysis, it becomes necessary to measure the areas under the nuclear resonance peaks. Region I contains peaks corresponding to the protons attached to doubly bonded carbon atoms, while region II corresponds to protons attached to carbon atoms forming only single bonds. The ratio of areas (I:II) should be 3:1 for compound A and 1:1 for compound B. The measured value of 2.9:1 leaves no doubt of the identity of the sample with structure A.

The sample was furnished through the courtesy of
Professor E. J. Corey, Chemistry Department, University of Illinois.

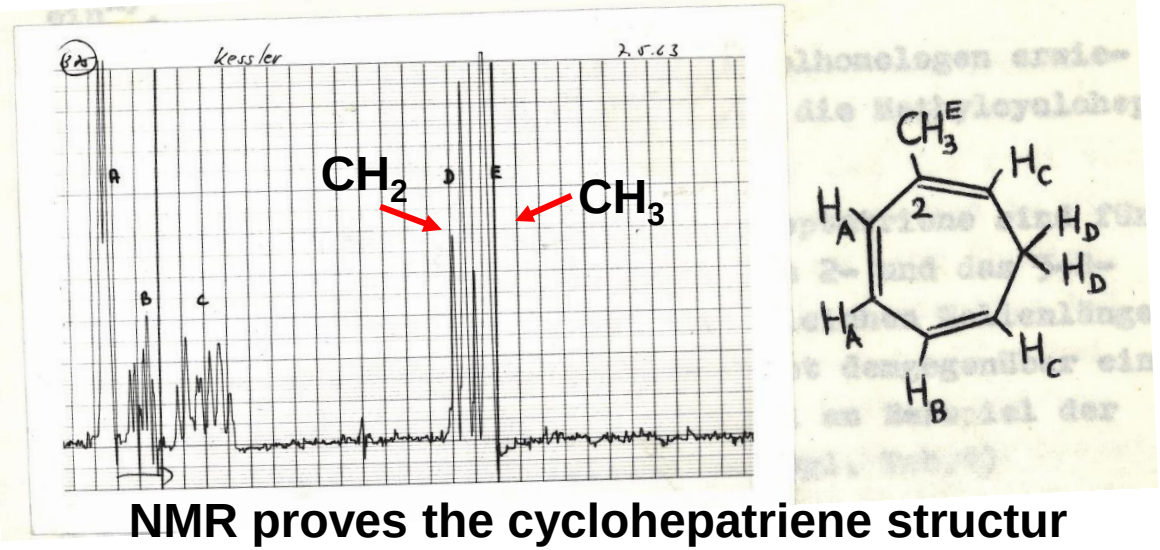
INCREASING MAGNETIC FIELD ⟶



eight years later

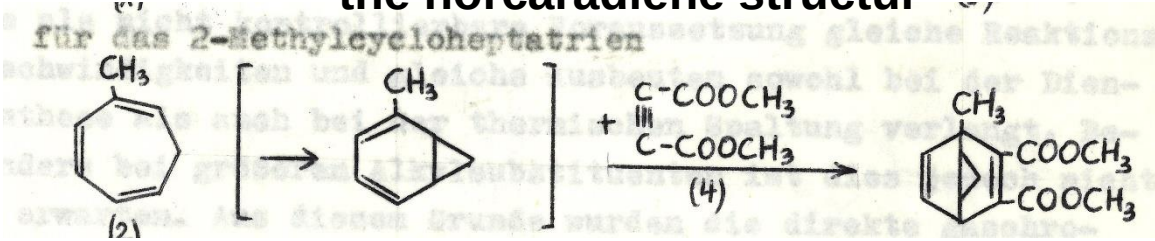


Methyl-cycloheptatrienes



NMR proves the cycloheptatriene structur

a chemical reaction would indicate the norcaradiene structur



NMR helps to elucidate the structure. Previously structure was elucidated by a chemical reaction. This would mislead in this case!

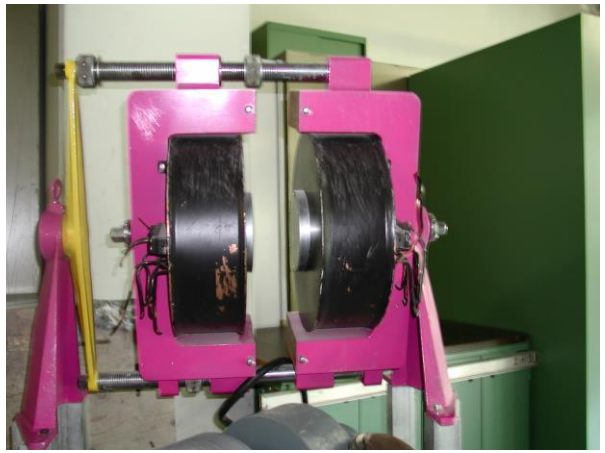
Usually we prefer nuclei with I = ½. **Most important nuclei for organic chemisty and biochemisty:**

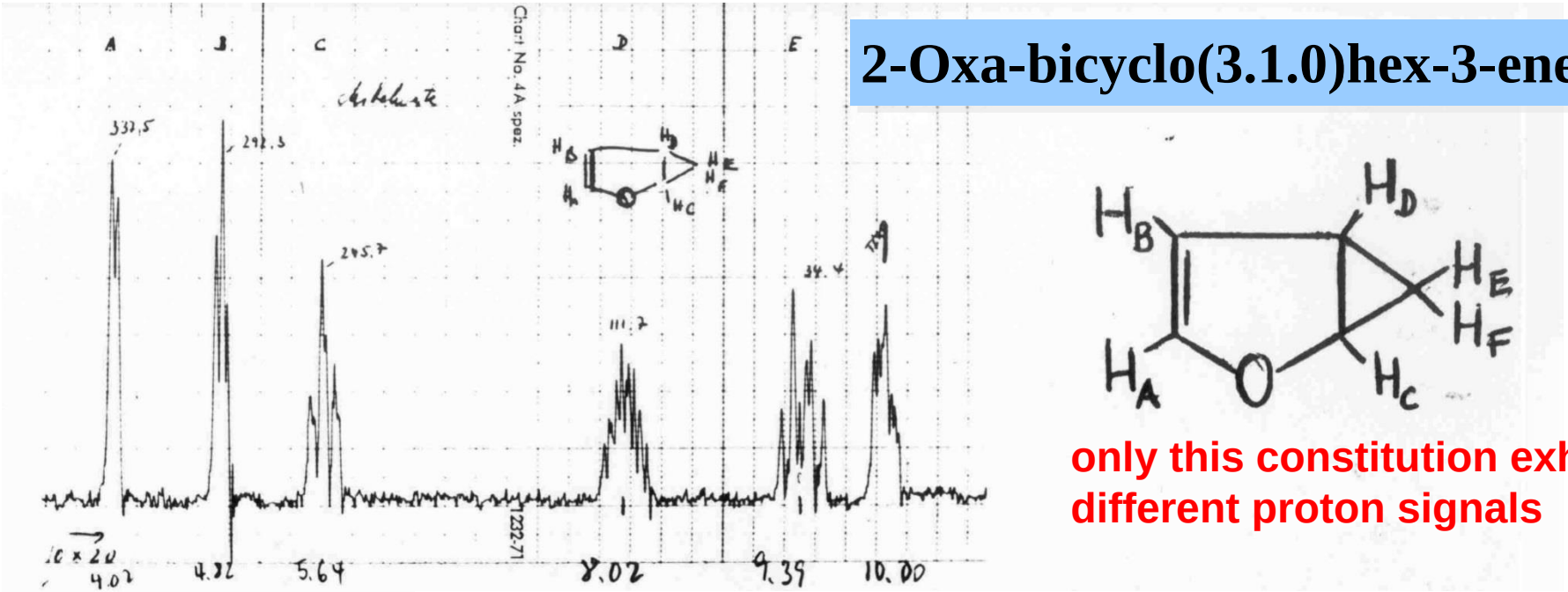
^{3}H 106,7 640 MHz 0

Isotope	γ (relative to ^{1}H = 100)	resonance fre-quency (at 14 T)	natural abundance	sensitivity (relative)
^{1}H	100	600 MHz	99.98 %	1.0
^{13}C	25	150 MHz	1.1 %	10^{-5}
^{15}N	-10	60 MHz	0.37 %	10^{-7}
^{19}F	94	546 MHz	100.0 %	0.8
^{29}Si	-20	119 MHz	4.7 %	10^{-3}
^{31}P	40	243 MHz	100.0 %	0.07

My first new compound, my first NMR spectrum, my first publication

^{1}H-NMR at 56.4 MHz



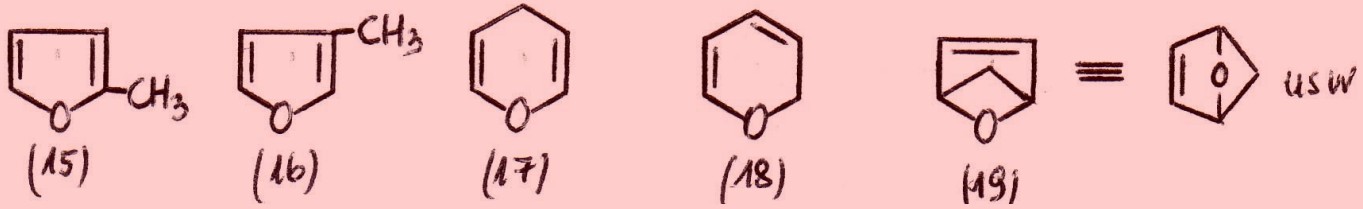


2-Oxa-bicyclo(3.1.0)hex-3-ene

only this constitution exhibit 6 different proton signals

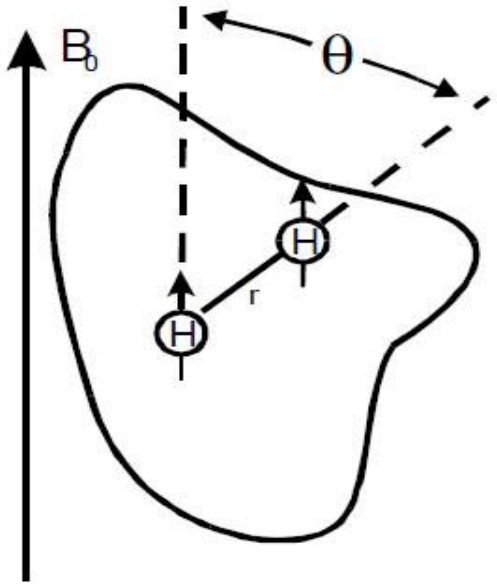
alternative structures:

excluded by NMR



E. Müller, H. Kessler , H. Fricke, H. Suhr *Tetrahedron Lett.* **1963**, 1047 - 1049

Coupling: The nuclei „feel“ the spin orientation of neighbored nuclei



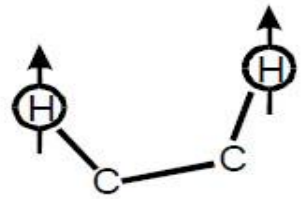
dipolar coupling = through space coupling it is proportional to

$$\frac{3\cos^2\theta - 1}{r^3}$$

For solid state NMR this term is zero, when the sample is rotated very fast about the “magic angle“ = 54,74 °

dipolar coupling disappears in spectra in solution as molecules are fast rotating. However, in solid state we observe very broad signals dipolar coupling

Scalar coupling



Scalar coupling (through bonds) depends from
- the number of bonds between the nuclei,
- the orientation of the bonds,
- hybridisation of the orbitals in the molecule

Relaxation of excited spins causes change in the population of neighbored spin stated which depend from the „through space distance“ The NOE.

The NOE is proportional to r^{-6}
With a reference distance in a molecule the distances of other nuclei can be determined.

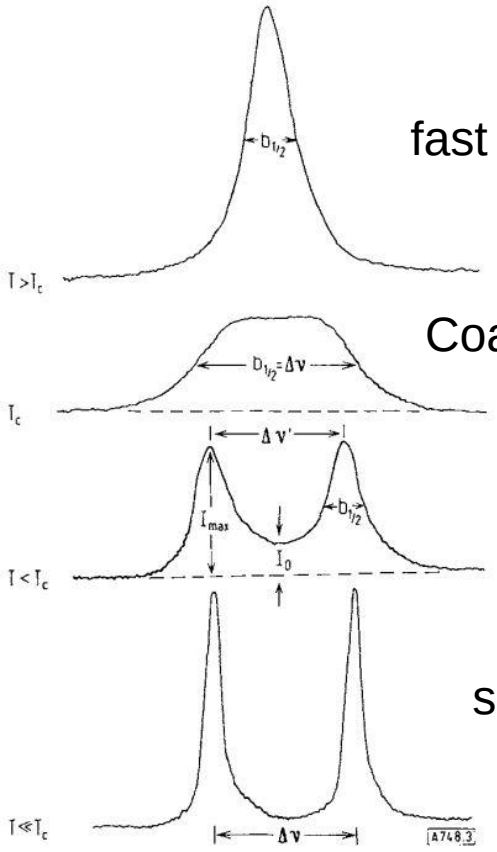
Most important for chemistry: chemical shift, J-coupling, dipolar coupling

NMR offers unique information about

- The number of structural and stereochemical different nuclei in a molecule
- Their „chemical nature“ (characterised by specific resonance frequencies)
- Connectivities of the atoms by scalar couplings (through bond couplings) **constitution**
- Stereostructures using the NOE (Nuclear Overhauser Effect) = distance dependent relaxation by neighbored protons (through space) **configuration**
- Chemical exchange (intramolecular mobility by time dependent resolution of signals (according to the Heisenbergs uncertainty principle two signals with different chemical shifts (corresponding to different energies) in different position within the molecules has to stay longer than the inversion of the frequency difference of the signals in the two positions. Rate constants for a thermal isomerisation can be determined by the line shape analysis of the coalescence phenomenon **conformation** **dynamics**

Thermal rearrangements within a molecule

According to Heisenberg frequency (energy) and positic
are canonically conjugated varables



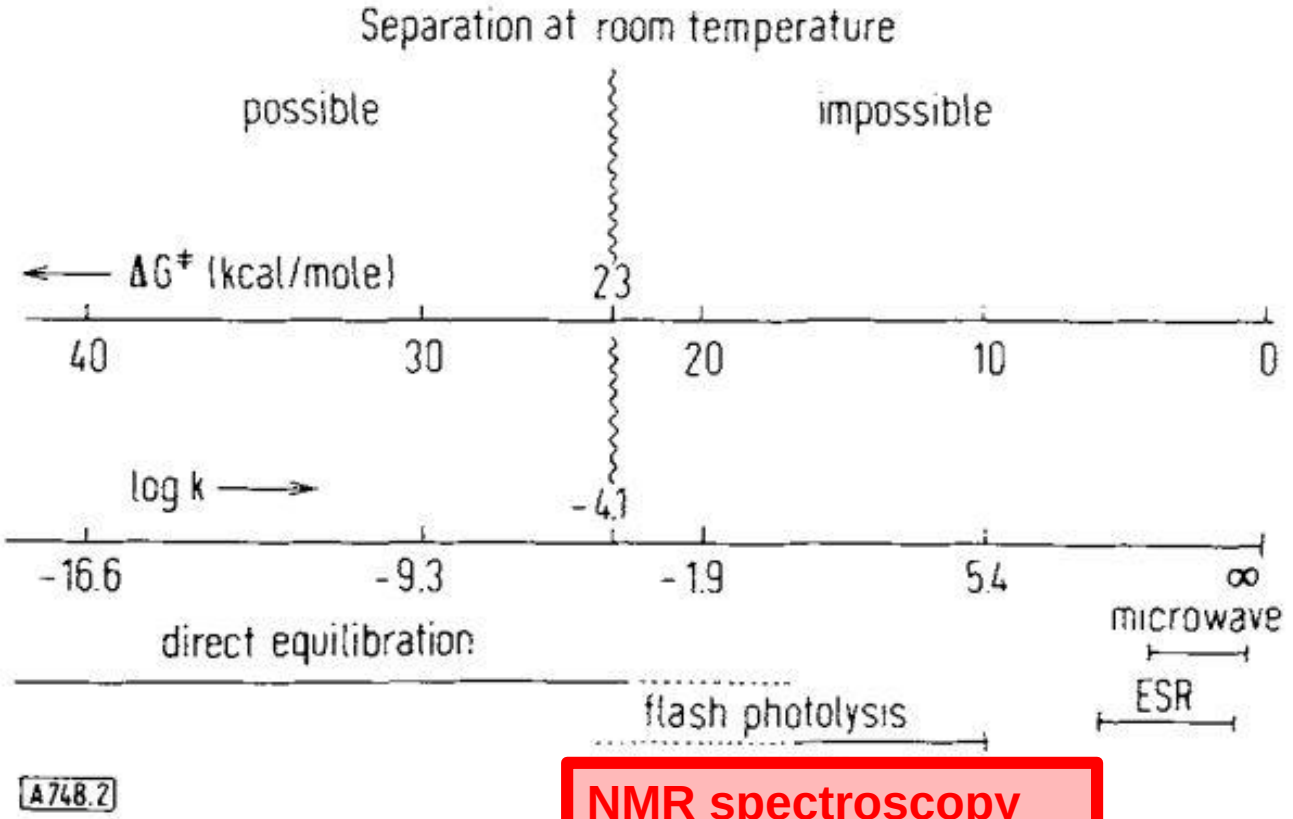
fast motion (high temperature)

Coalescence, when $k = \pi\Delta\nu/ 2^{1/2}$

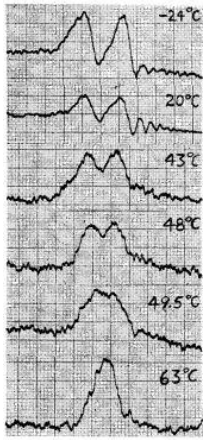
slow motion (low temperature)

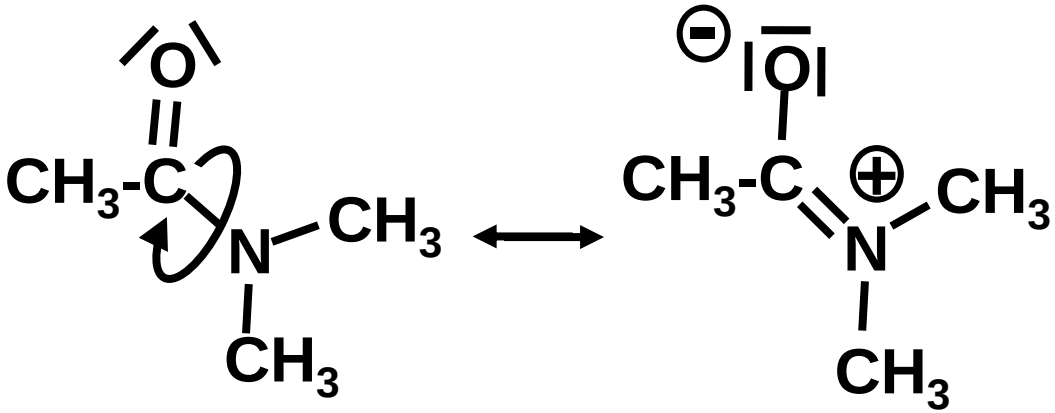
Free activation enthalpy $\Delta G^{\ddagger}$

$$k_r = \frac{k_B T}{h} \exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right)$$



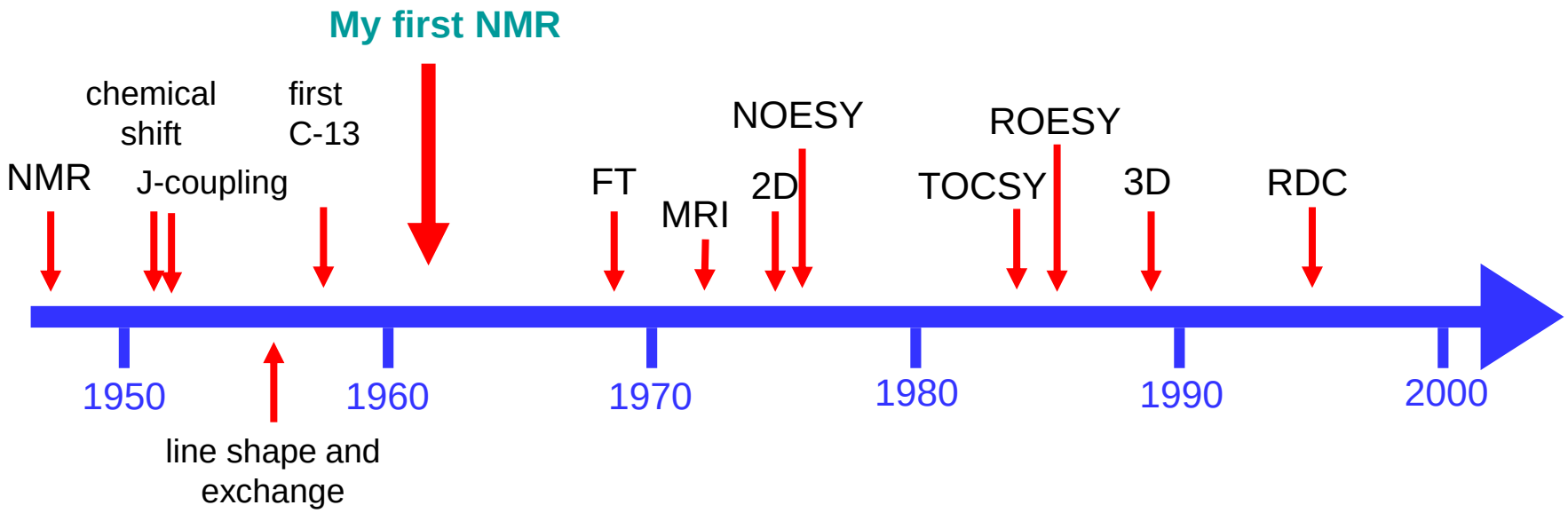
NMR spectroscopy



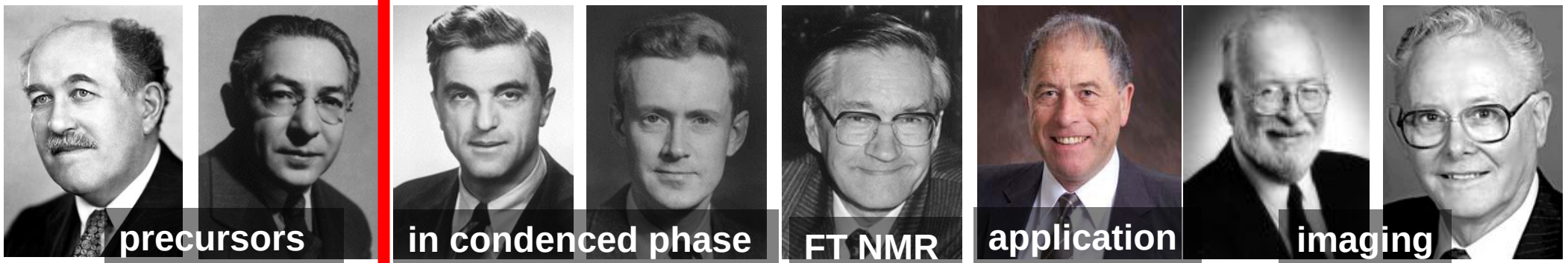


H.S. Gutowsky, C.H. Holm, *J.Chem.Phys*.**1956**, *25*, 1228-1234

More than 80 years NMR spectroscopy



Nobel prize winners



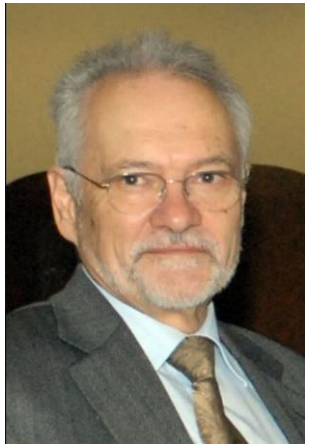
Stern 1943 | Rabi 1944 | Bloch 1952 | Purcell 1952 | Ernst 1991 | Wüthrich, 2002 | Lauterbur 2004 | Mansfield 2004

The new technology: FT-NMR published 1966, the year of my Ph.D. dissertation

1966 R.R. Ernst, W.A. Anderson, *Rev. Sci. Instrum*. **1966**, *37*, 93. rejected from J.Chem.Phys. **Nobel-Prize-Award-Paper!**

Richard Ernst

Tony Keller



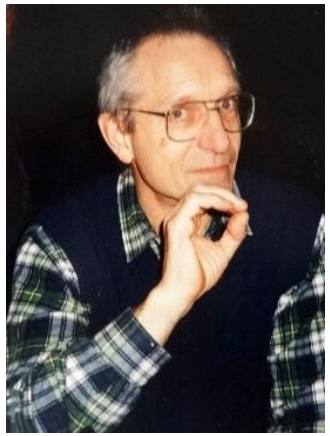
FT-NMR

1971 When I came to Frankfurt I ordered the first FT NMR in Germany, against the recommendation of my NMR colleagues in Frankfurt:
„FT NMR is not useful, as we cannot decouple spin systems.“

Already in 1972/73 Tony Keller realized also homonuclear decoupling in the Bruker spectrometers

Later I wanted to do 2D NMR

Jean Jeener



2D-NMR

1971 Introduced the 2D NMR at a conference in Basco Polje 1971 by Jean Jeener

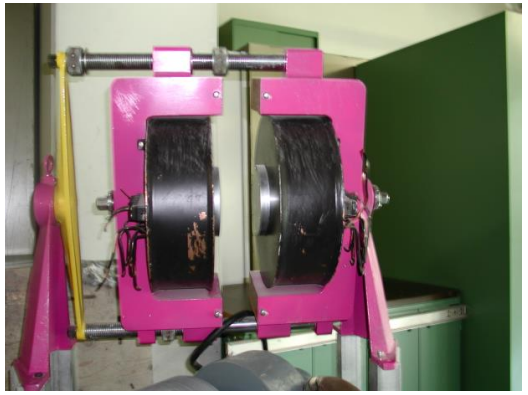
1975/76 Experimental verification by the Ernst group

I became interested in the new 2D NMR

W. P. Aue, E. Bartholdi, R. R. Ernst, ***J. Chem. Phys. 64*** (1976) 2229-2246.

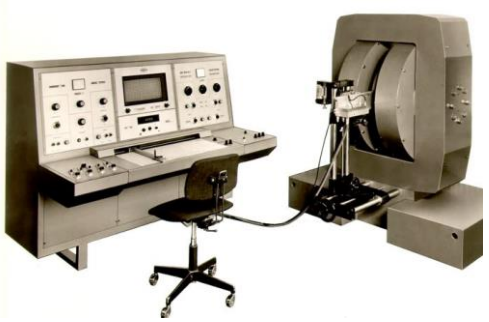
Increasing equipments from Tübingen via Frankfurt to Garching (Munich)

1962 Tübingen



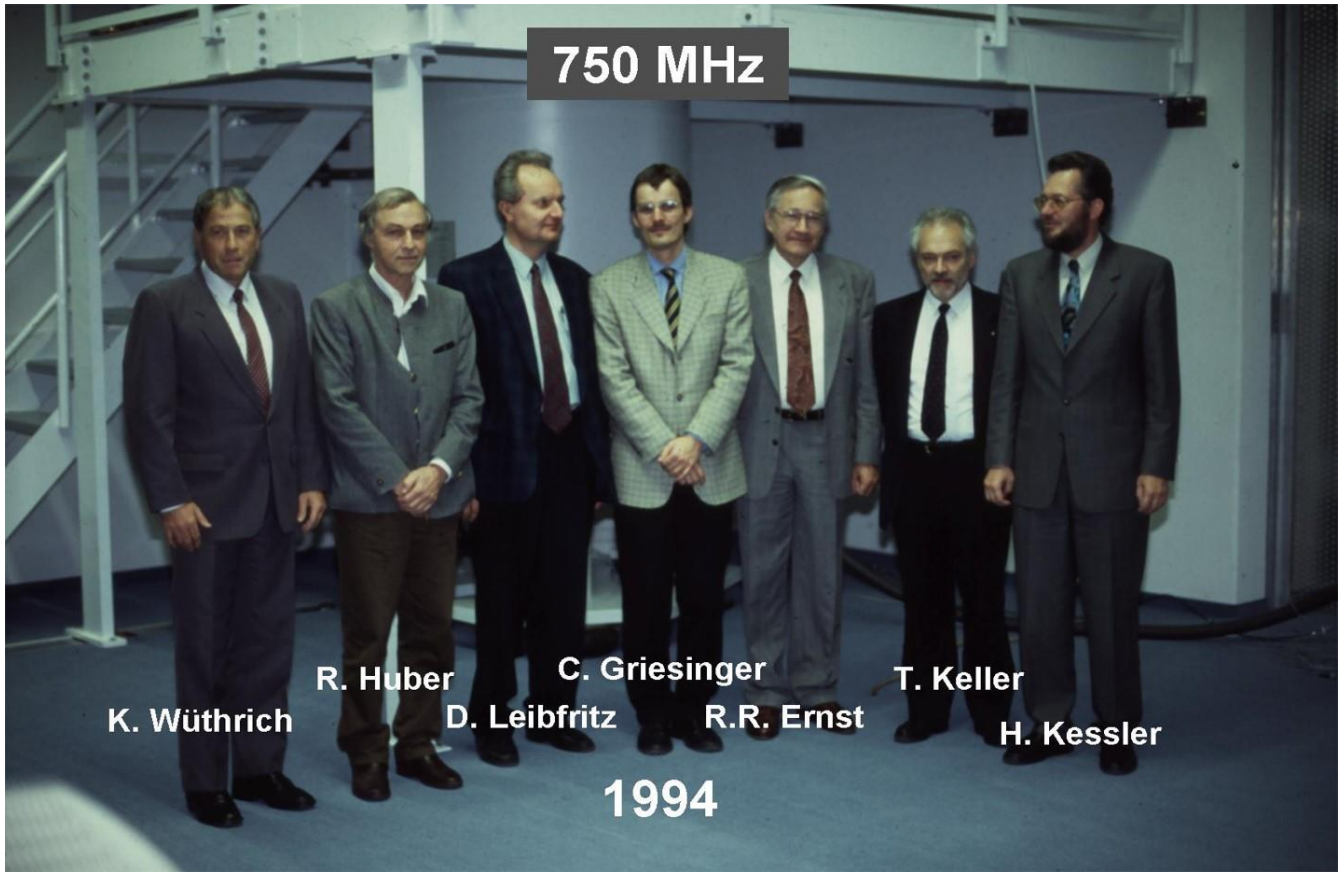
1962
Varian 56,4 MHz

1971 Frankfurt



1971
FT-NMR Bruker 90 MHz

1989: Garching

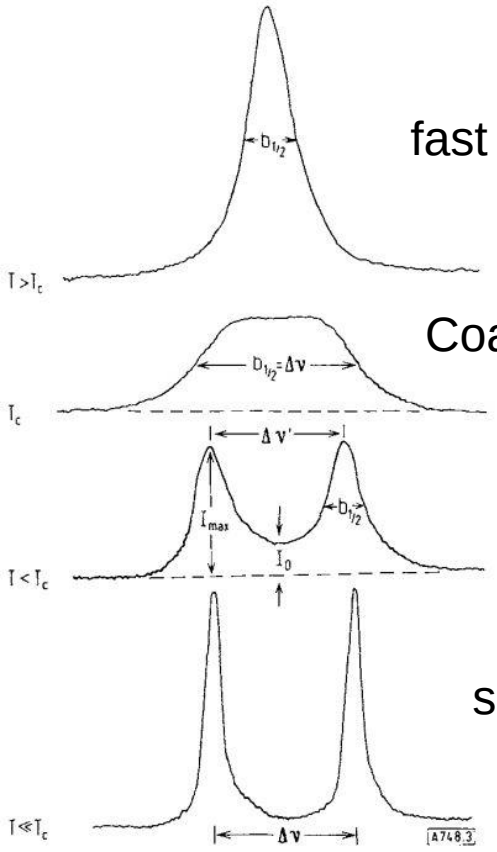


2004
900 MHz

2018 BNMRZ
with 1,2 GHz 2022

Thermal rearrangements within a molecule

According to Heisenberg frequency (energy) and positic
are canonically conjugated varables



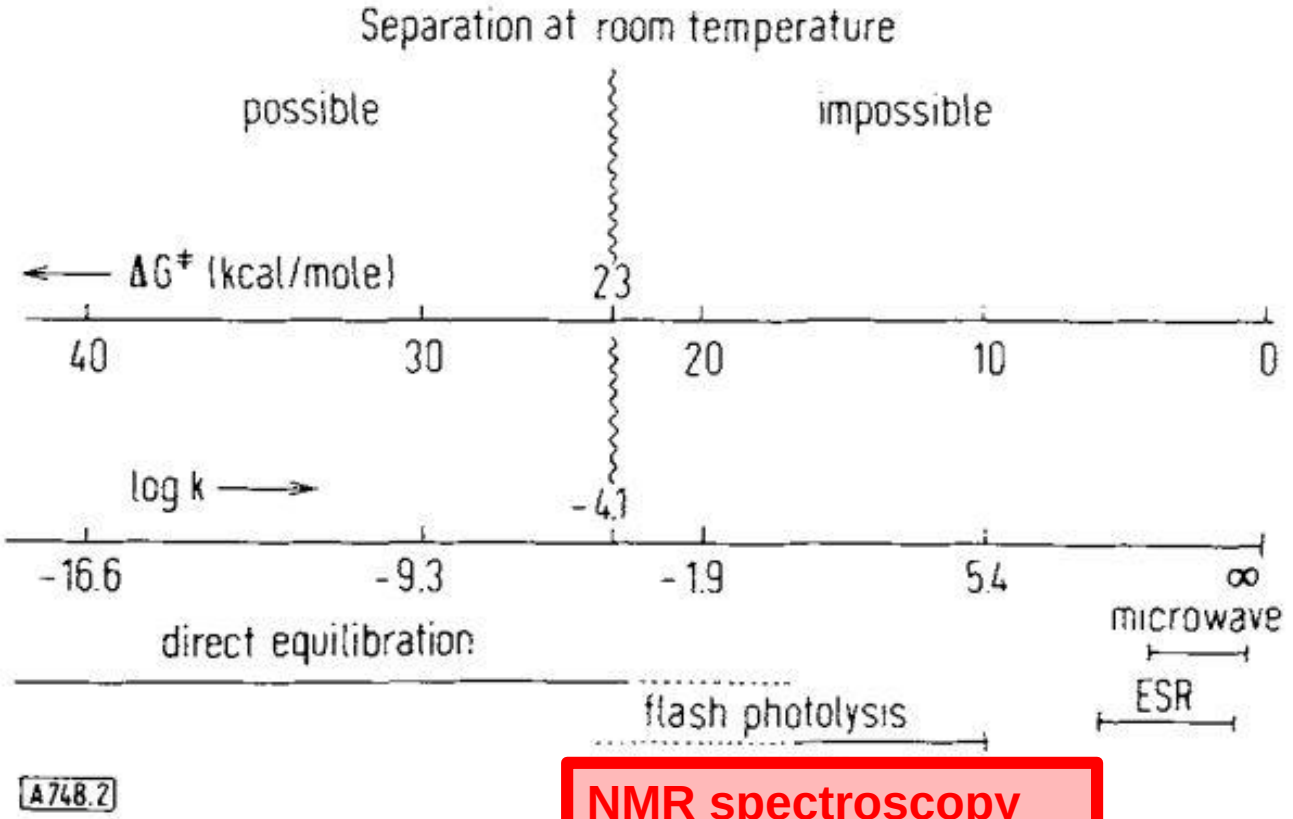
fast motion (high temperature)

Coalescence, when $k = \pi\Delta\nu/ 2^{1/2}$

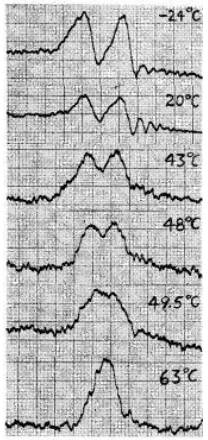
slow motion (low temperature)

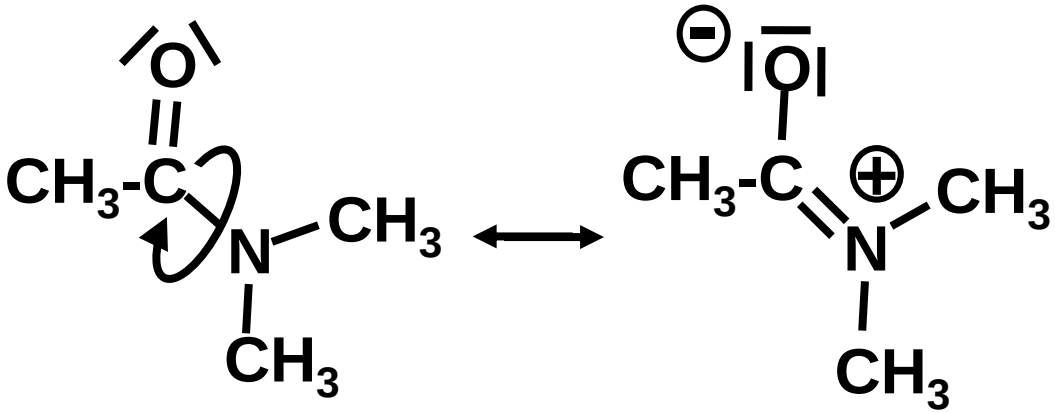
Free activation enthalpy $\Delta G^{\ddagger}$

$$k_r = \frac{k_B T}{h} \exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right)$$



NMR spectroscopy



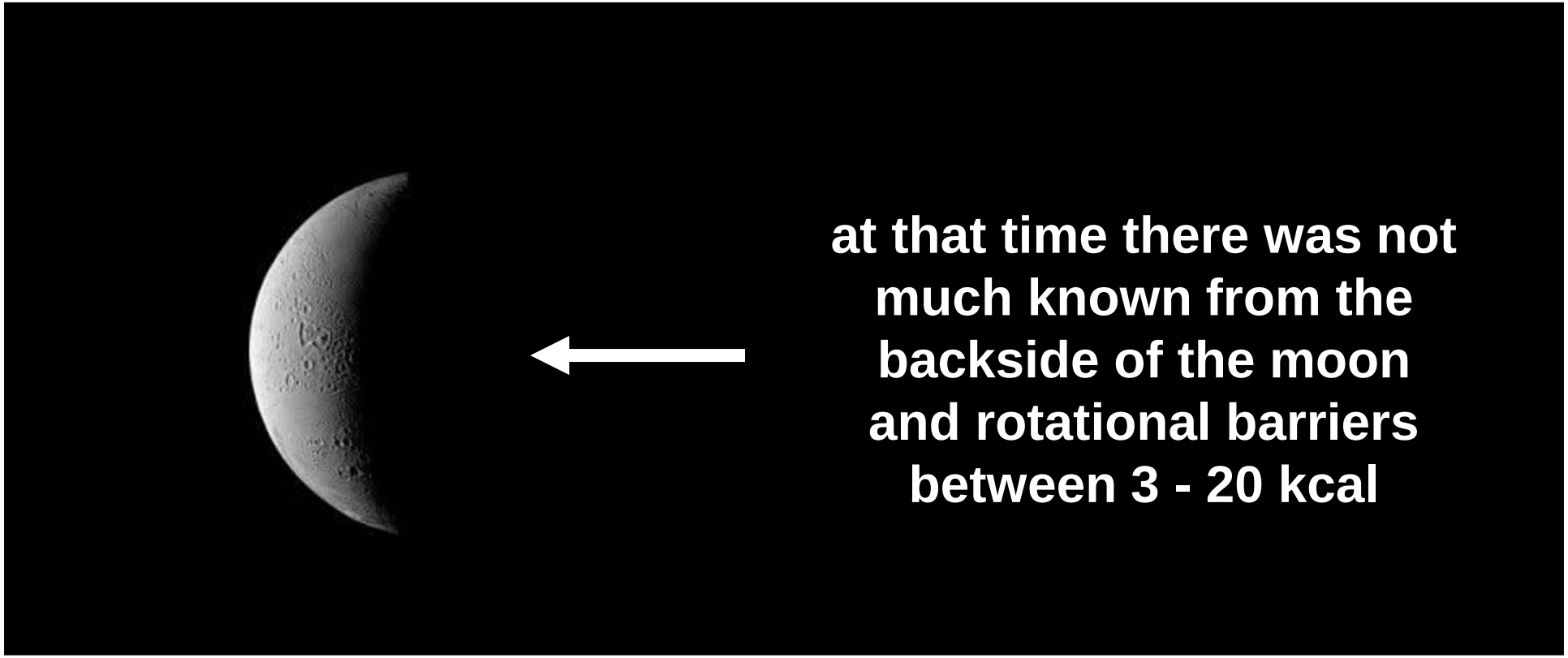


H.S. Gutowsky, C.H. Holm, *J.Chem.Phys*.**1956**, *25*, 1228-1234

60 years ago

I became interested in intramolecular mobility

e.g. barriers of rotations about single and double bonds



My interest 1966 – late 70ies: intramolecular mobility - mechanistic chemistry was “in”

slow rotaton about single bonds

fast rotations about double bonds

mechanism of syn-anti isomerization (proof of inversion)

ring inversions

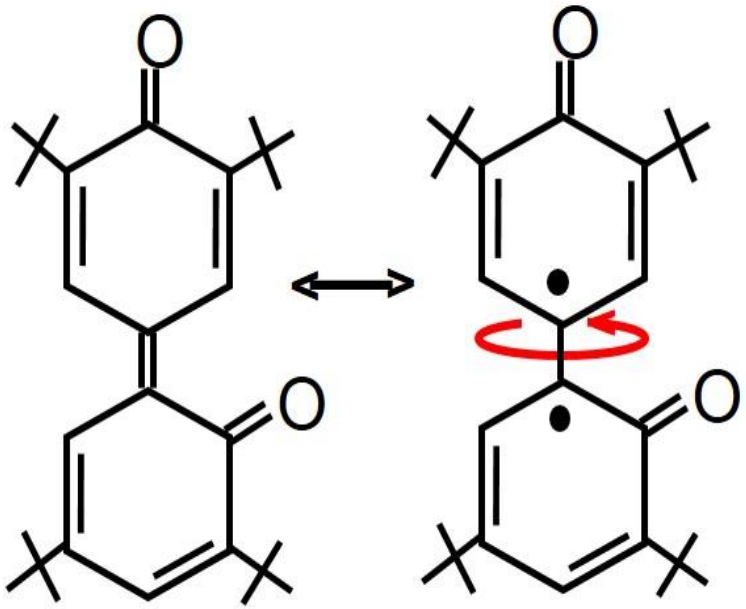
fast valence isomerization

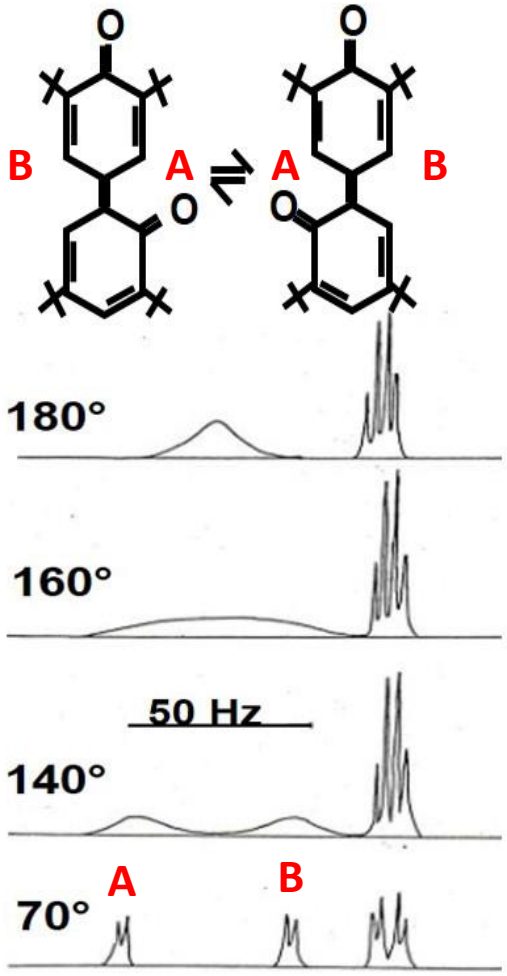
ion pair recombinations

H. Kessler; Detection of Hindered Rotation and Inversion by NMR Spectroscopy;
Angew. Chem. Int. Ed. **1970,** *9*, 219-235.

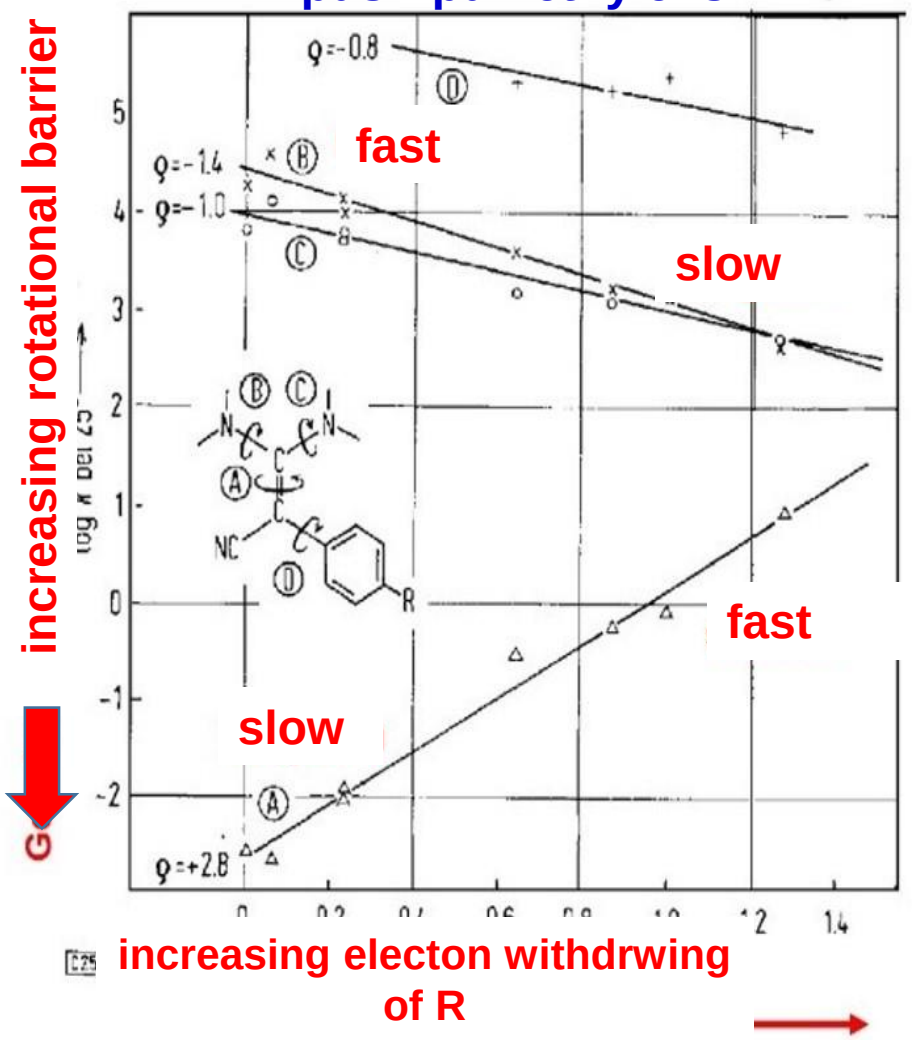
Innermolecular mobility: fast rotations about double bonds

1966





push-pull-ethylens

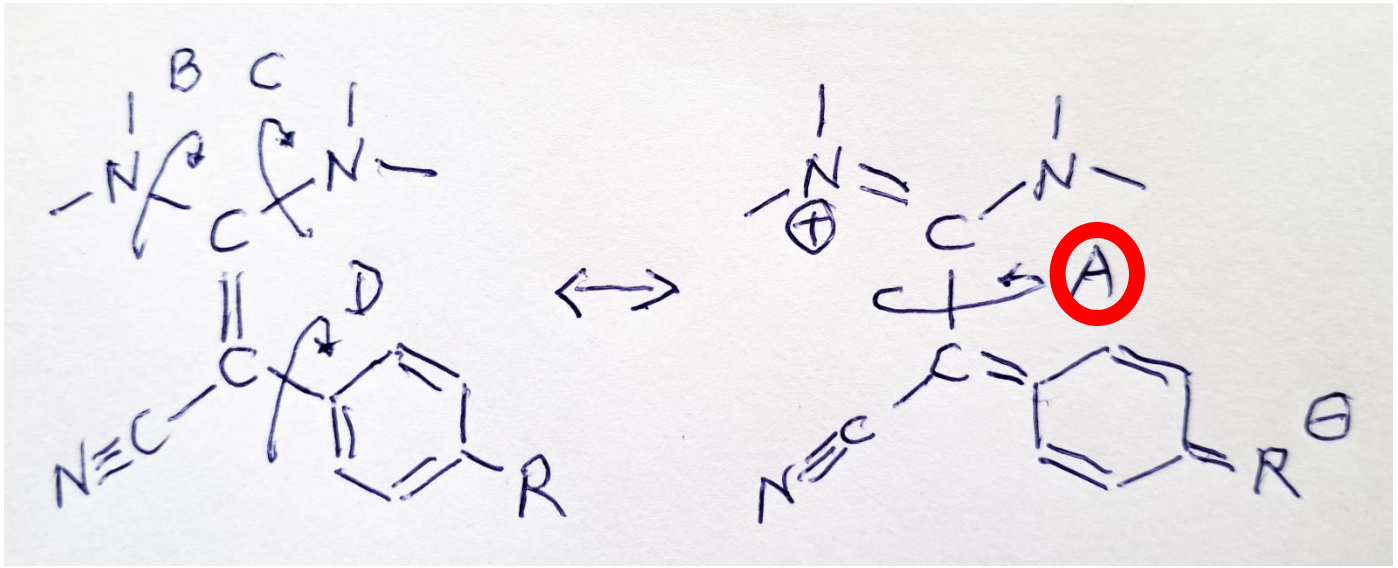


1970

H. Kessler, A. Rieker, *THL* **1966**, 5257-5262.

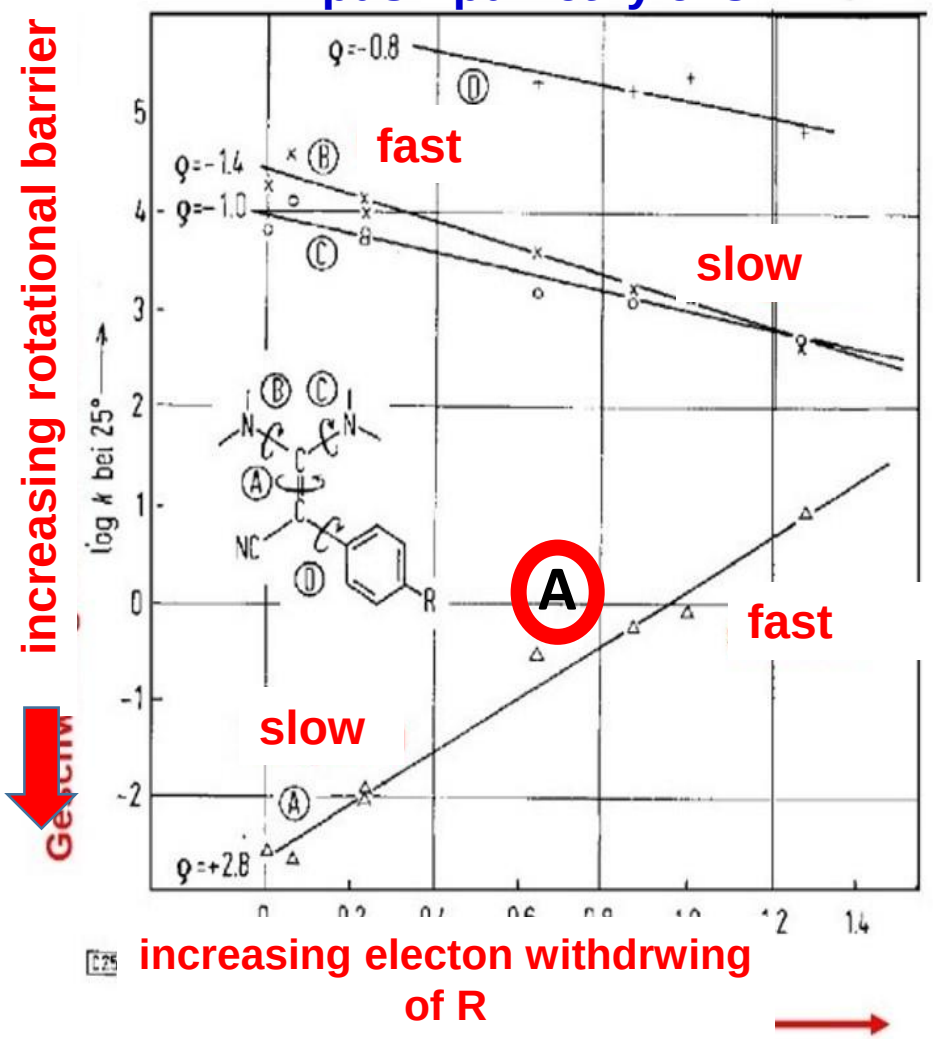
H. Kessler. *Chem.Ber*. **1970**, *103*, 973-985.

Innermolecular mobility: fast rotations about double bonds



increasing electon withdrwing of R

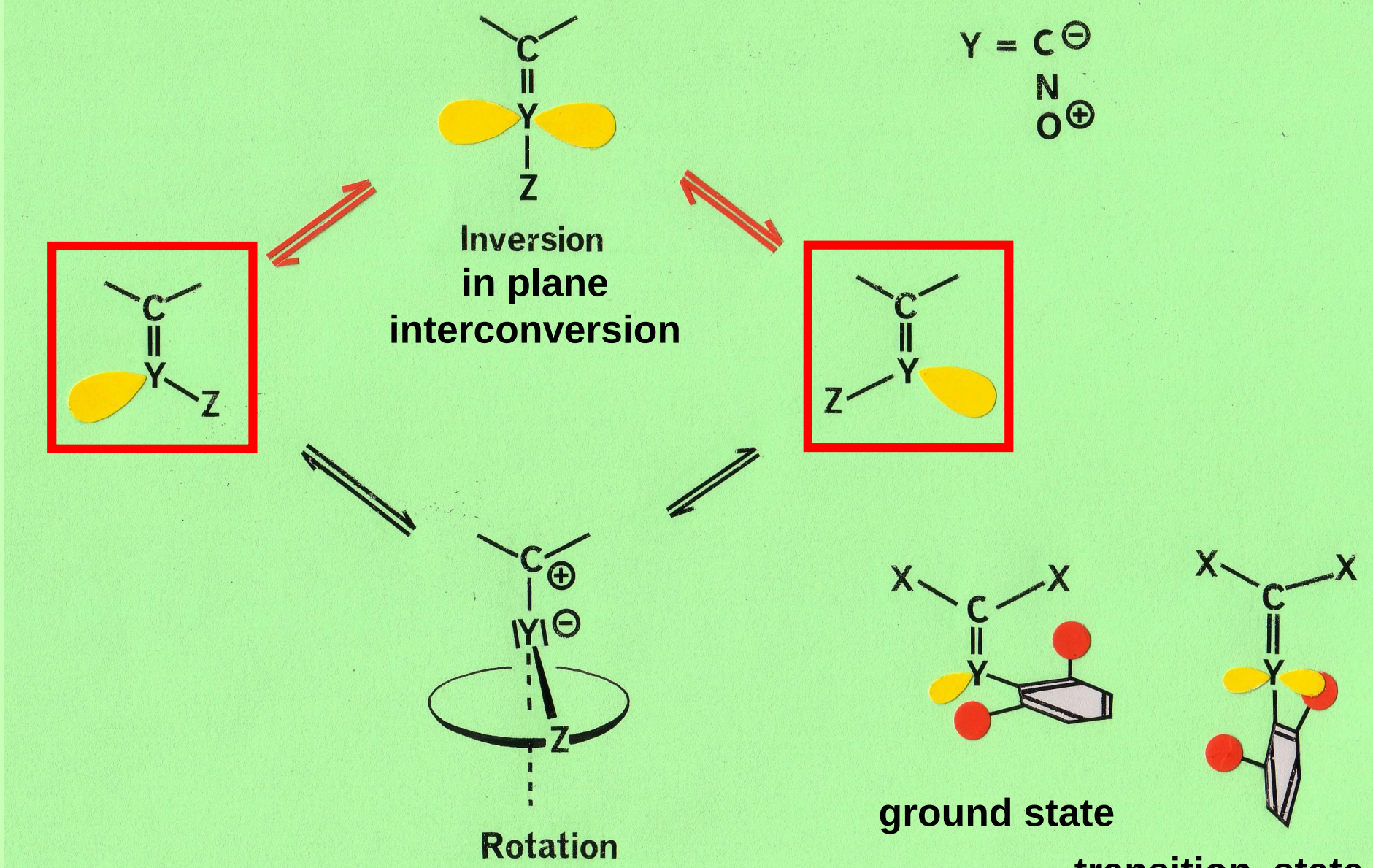
push-pull-ethylens



1970

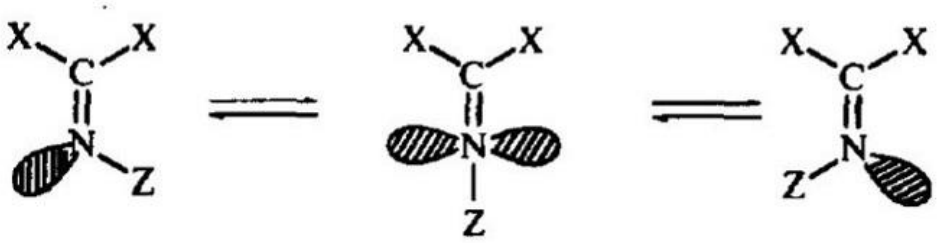
H. Kessler. *Chem.Ber*. **1970**, *103*, 973-985.

Alternative pathways of syn-anti Isomerization

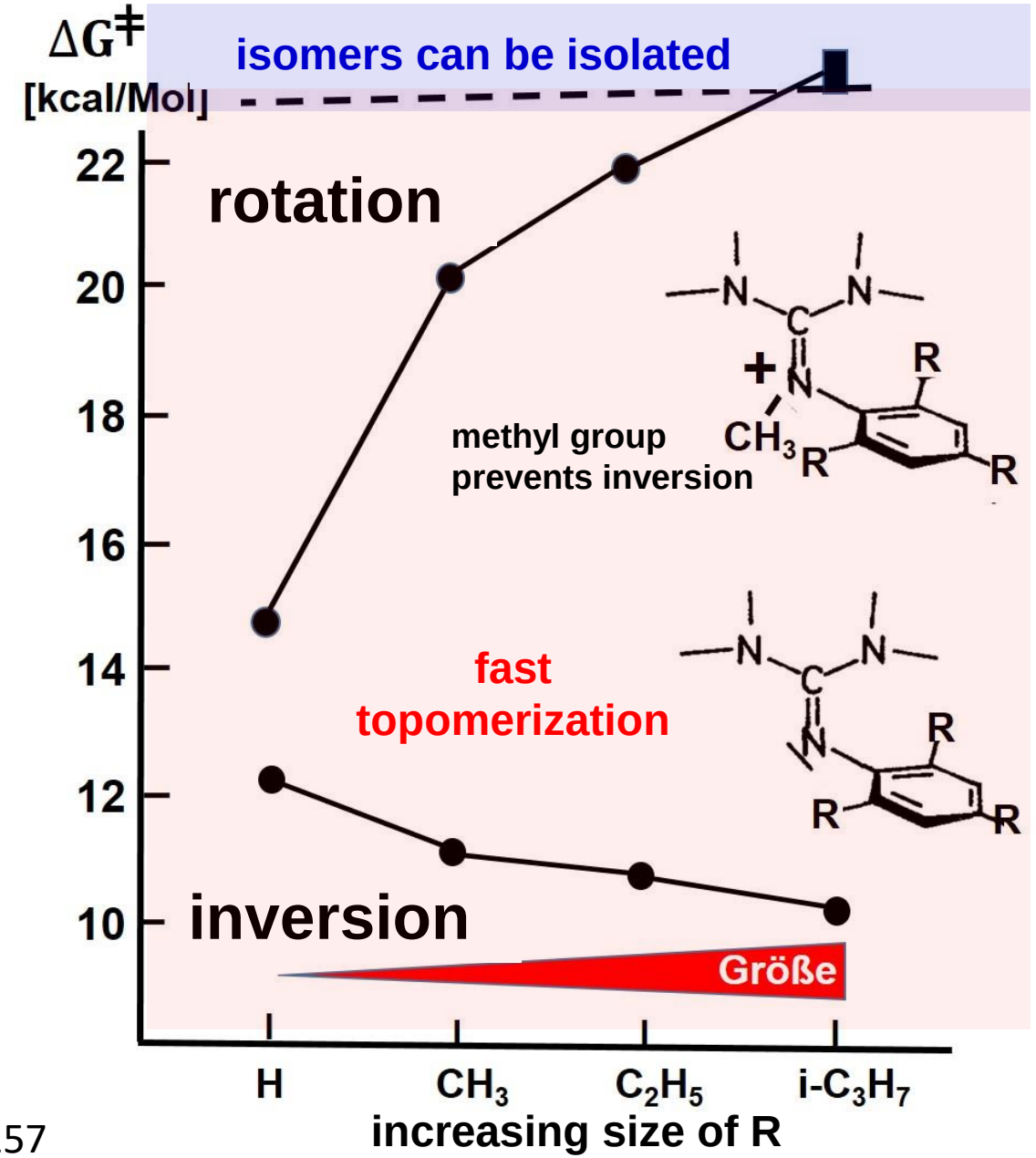


Substituent effect on the syn-anti-isomerization barrier proves inversion mechanism

Dieter Leibfritz
my first PH.D.
mtudent



planar inversion



steric hindrance in the transition state larger

steric hindrance in the ground state larger

H.Kessler, *Tetrahedron Lett*. **1968**, *24*, 5133-5144;
H.Kessler, D. Leibfritz, *Chem.Ber.* **1971**,*104*, 2143-2157

Some topics of intramolecular mobility by NMR

Physical-Organic Chemistry was „in“ (a hot topic) at that time

- **slow rotations about single bonds**
- **fast rotations about double bonds**
- **pyramidal and planar inversion**
- **barriers of ion recombinations**
- **[3,3]sigmatropic rearrangements**
- **ring inversions**

Influence of size and donor-acceptor properties by substitution

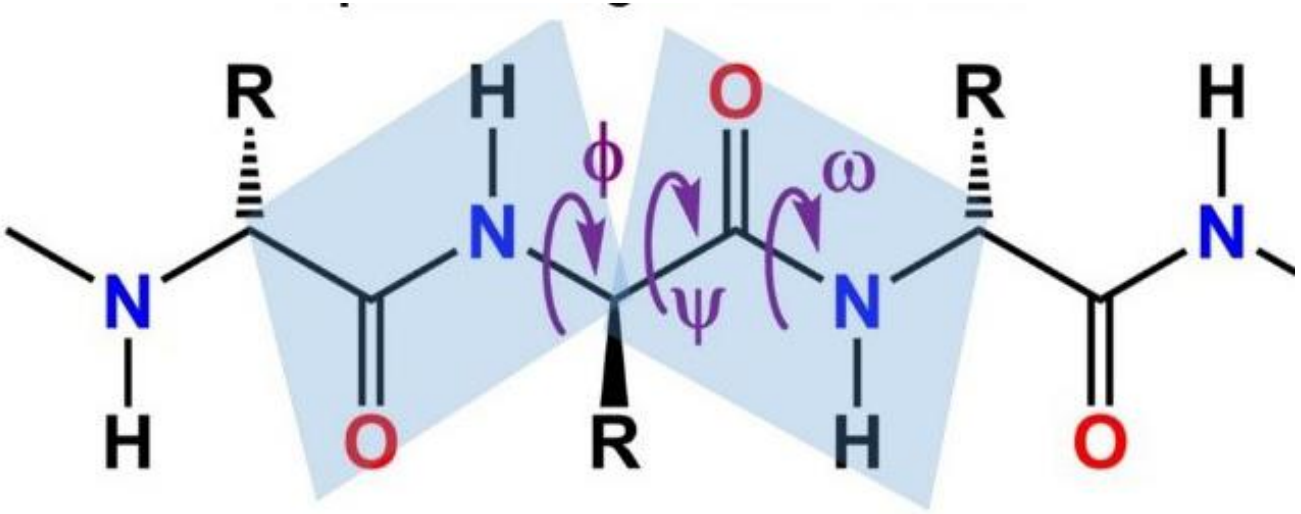
Review: H. Kessler, Detection of Hindered Rotation and Inversion by NMR Spectroscopy; *ACIE* **1970,** *9*, 219-235.

1965-1970

I determined many different processes, but after 3 years in the field most interesting barriers were known or predicable; further studies became routine (= boring)

Looking for a topic where stereochemistry is important I decided to study

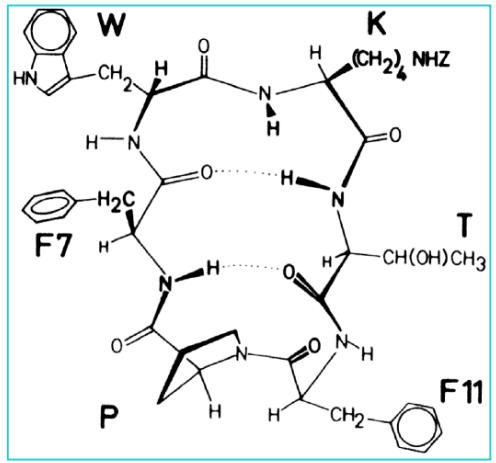
conformation of peptides

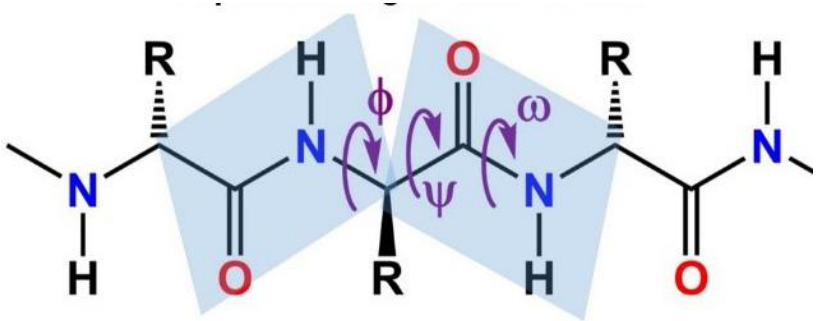


Peptides (miniproteins) are biologically very important (e.g. as hormones)

However: they are very flexibel

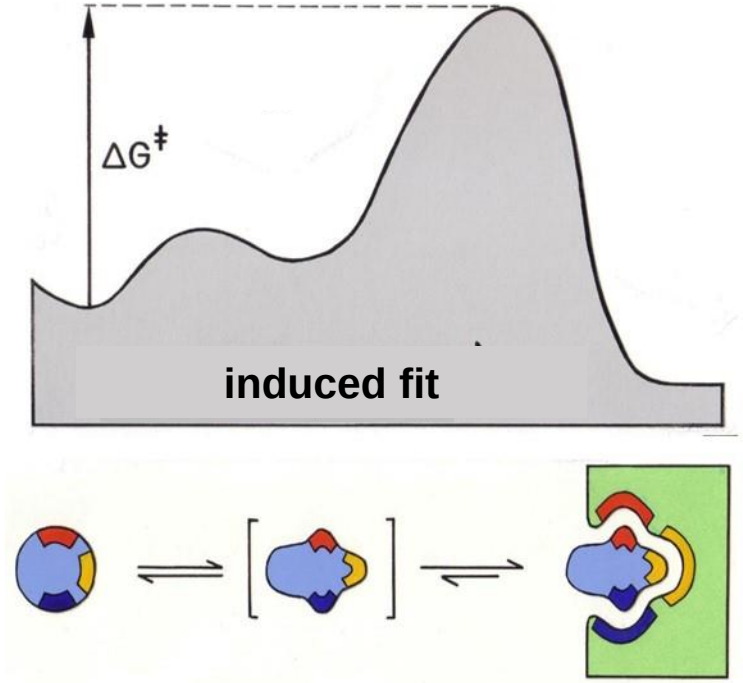
Hence we synthesised cyclic peptides

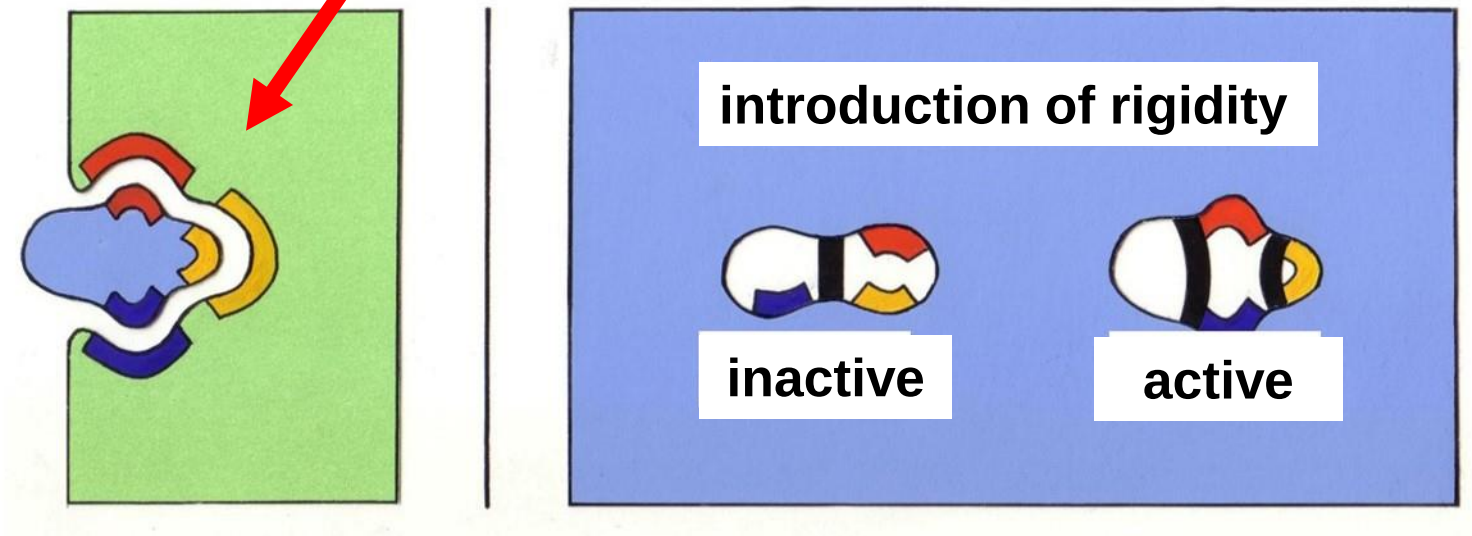




Search for the „bioactive conformation“

Conformational change by binding





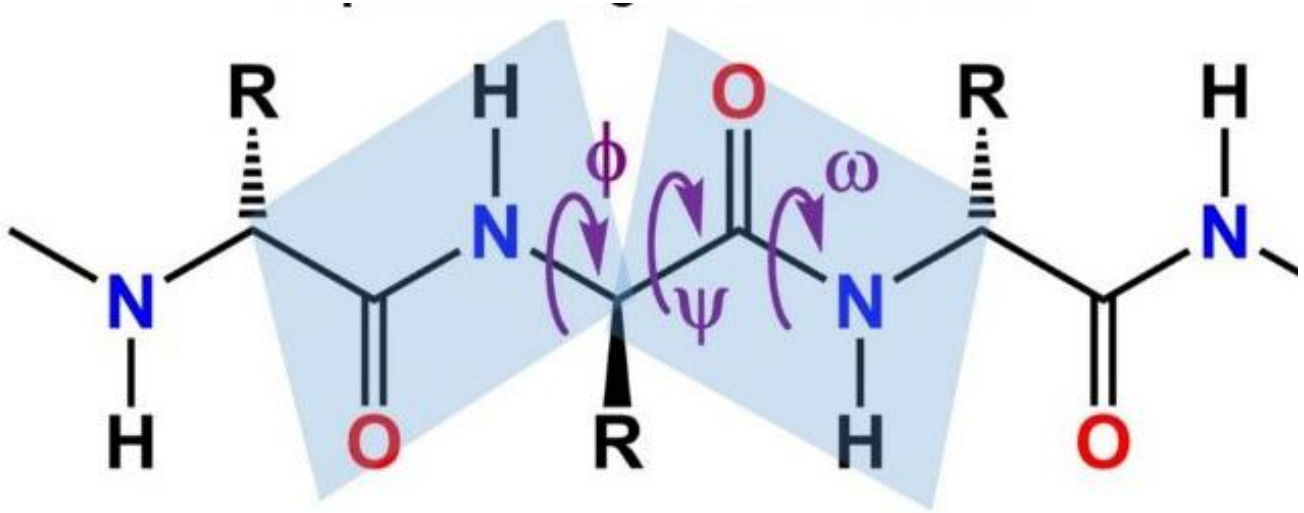
Victor Hruby had the same idea at that time

H. Kessler *ACIE*. **1982,** *21*, 512-523.
V. Hruby *Life Sci*.**1982**, *31*, 189-199

1965-1970

I determined many different processes but after 3 years in the field most interesting barriers were known or predicable; further studies became routine (= boring)

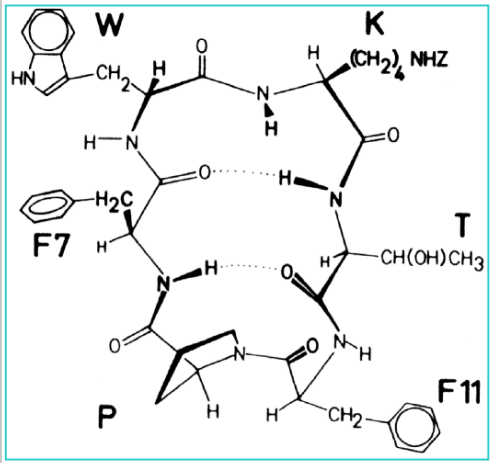
Looking for a topic where stereochemistry is important I decided to study conformation of peptides



Peptides (miniproteins) are biologically very important (e.g. as hormones)

However: they are very flexibel

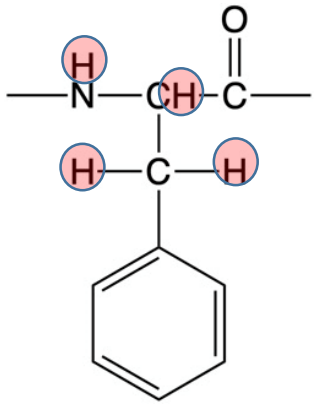
Hence we synthesised cyclic peptides



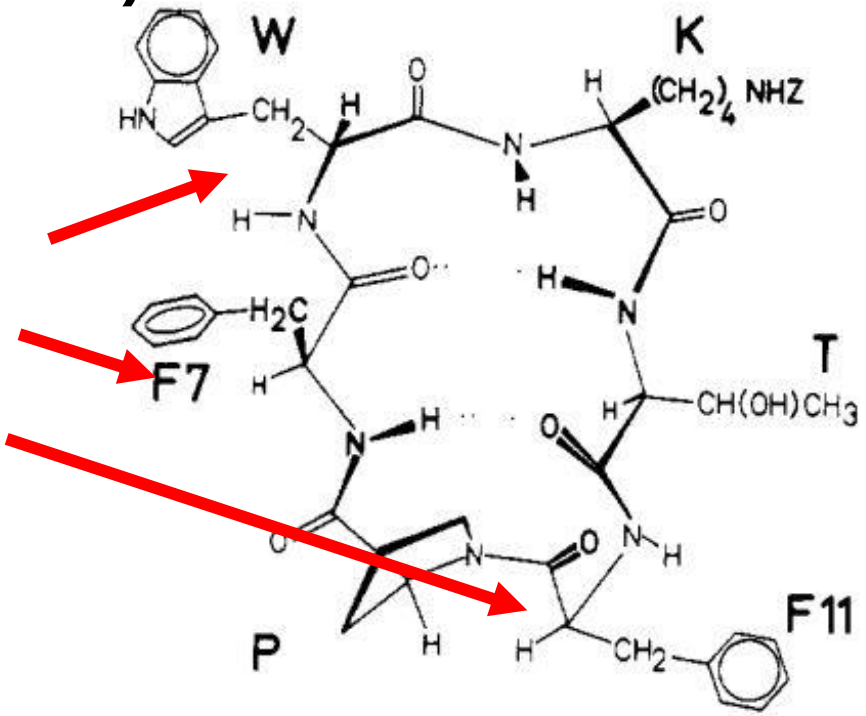
Example: the Veber-Hirschmann-Peptide (Merck USA)

A superavtive Somatostatin-derivative with cytoprotective properties

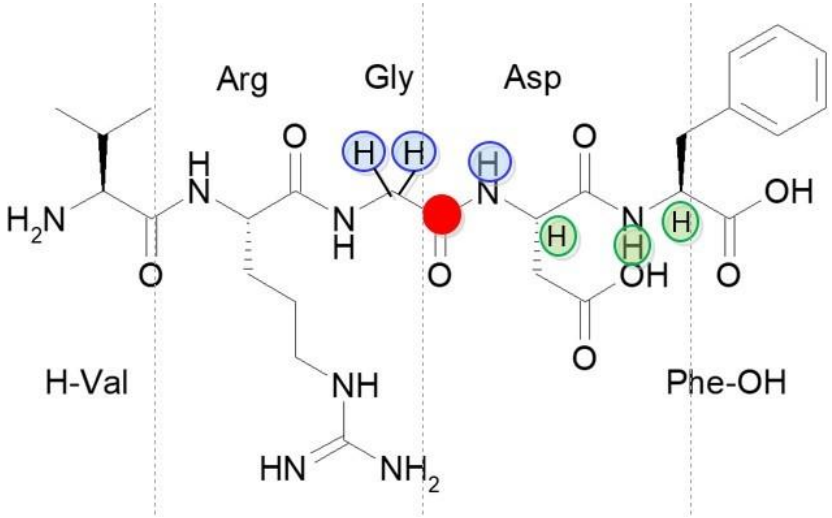
Assignment of Signales to the constitution

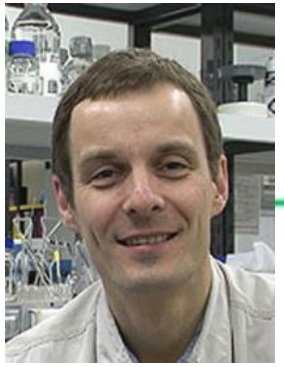


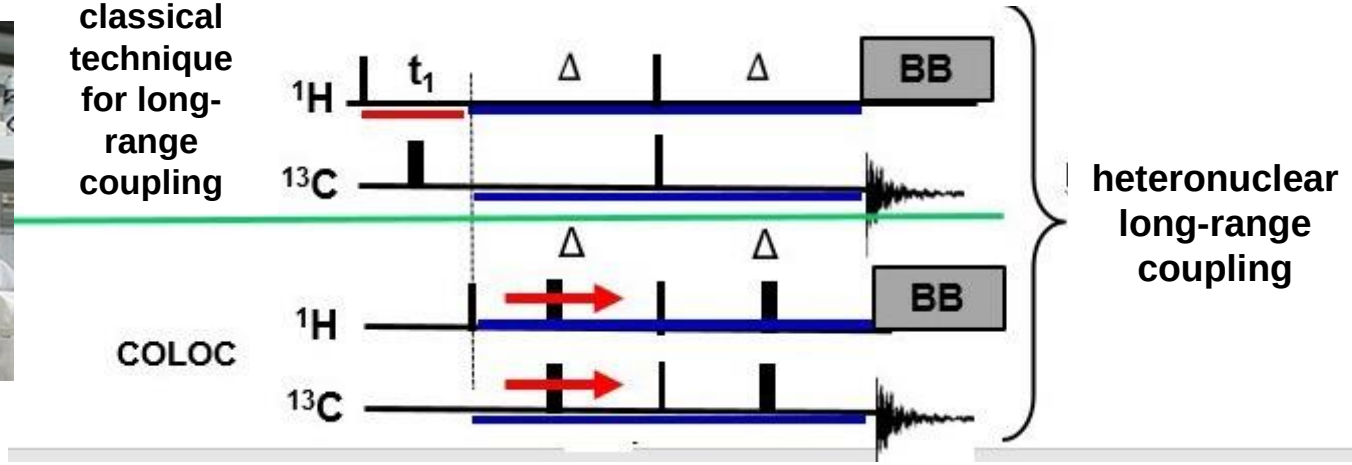
The spin system occurs 3 times in the molecule. We have to assign them.



Sequencing via NOE and/or COLOC: ^{13}C as „Spy“

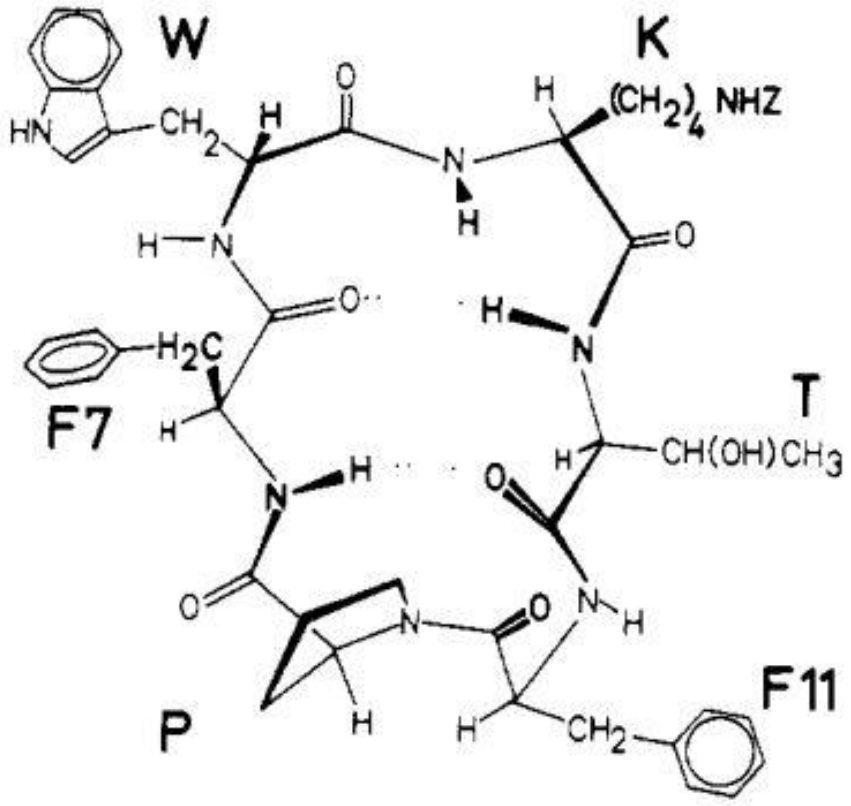






COLOC: H.K., C. Griesinger, J. Zarbock, H. R. Loosli, *J. Magn. Reson.* **1984,** *57*, 331-336.

NOE: C.J.R. Jones …W.A. Gibbons, *Biophys.J.* **1978**,24,815-832; A.Dubs, G. Wagner, K. Wüthrich, *Biophys. J.* **1979**, 24, 177-194.



C-H-H pulse sequence

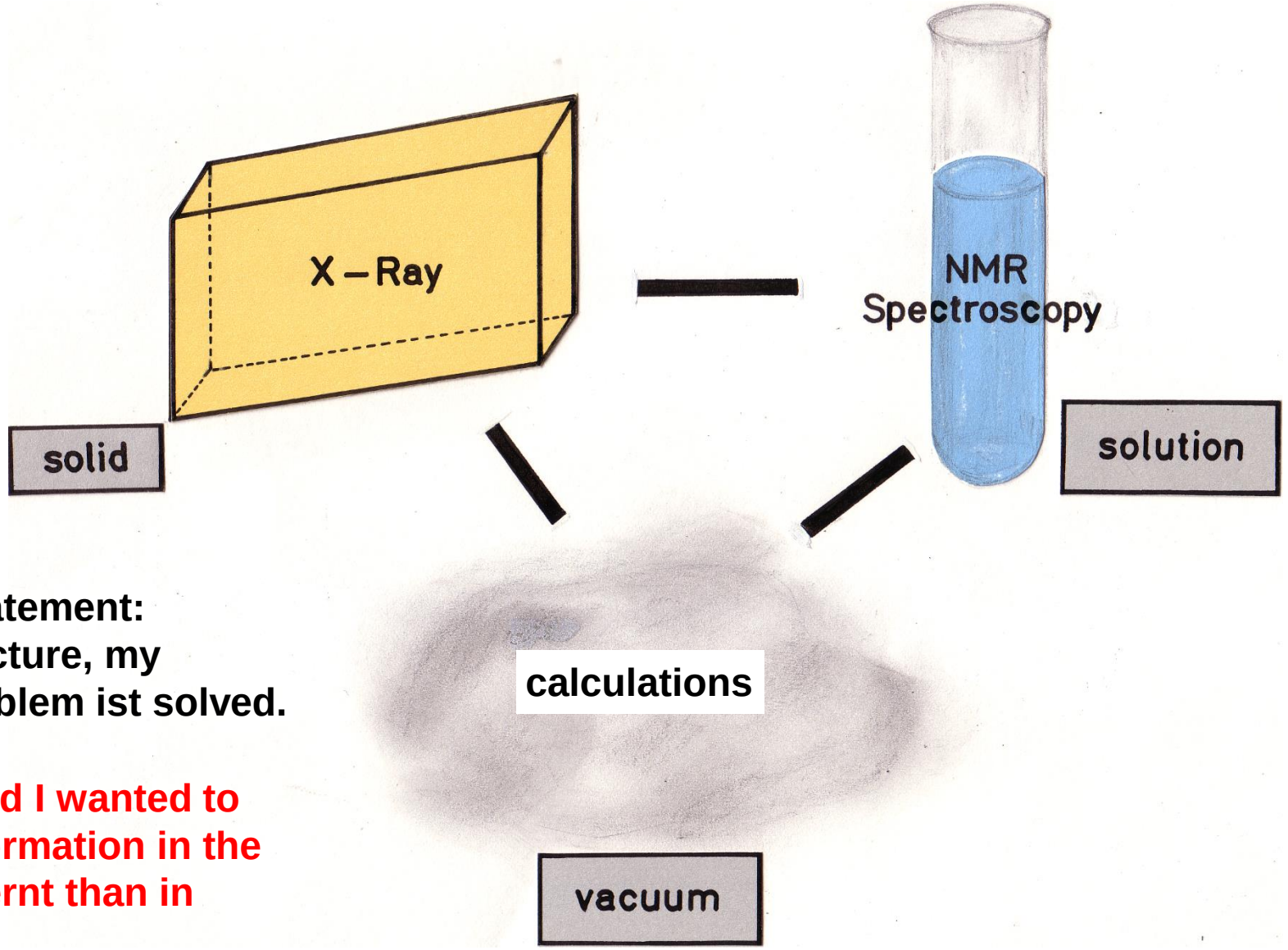
and conformation of the *Veber-Hirschmann-Peptide*

High biological activity for the receptor for the peptide hormone somatostatin

H. Kessler, M. Bernd, H. Kogler, J. Zarbock, O. W. Sørensen, G. Bodenhausen, **R. R. Ernst**; Relayed Heteronuclear Correlation Spectroscopy and Conformational Analysis of Cyclic Hexapeptides Containing the Active Sequence of Somatostatin; *J. Am. Chem. Soc.* **1983,** *105*, 6944-6952

Later we found a way to convert it into a drivative with oral activity (very important for peptidic drugs)

Is the **Structure** in Crystal and Solution Identical ?



Often I heard the statement:
I have an X-ray structure, my conformational problem ist solved.

This is nonsense and I wanted to prove that the conformation in the crystal may be differnt than in solution

Unequivocal proof that conformation in solution may be different from the crystal conformation

Step 1

Search a system with a reasonable high barrier between conformations

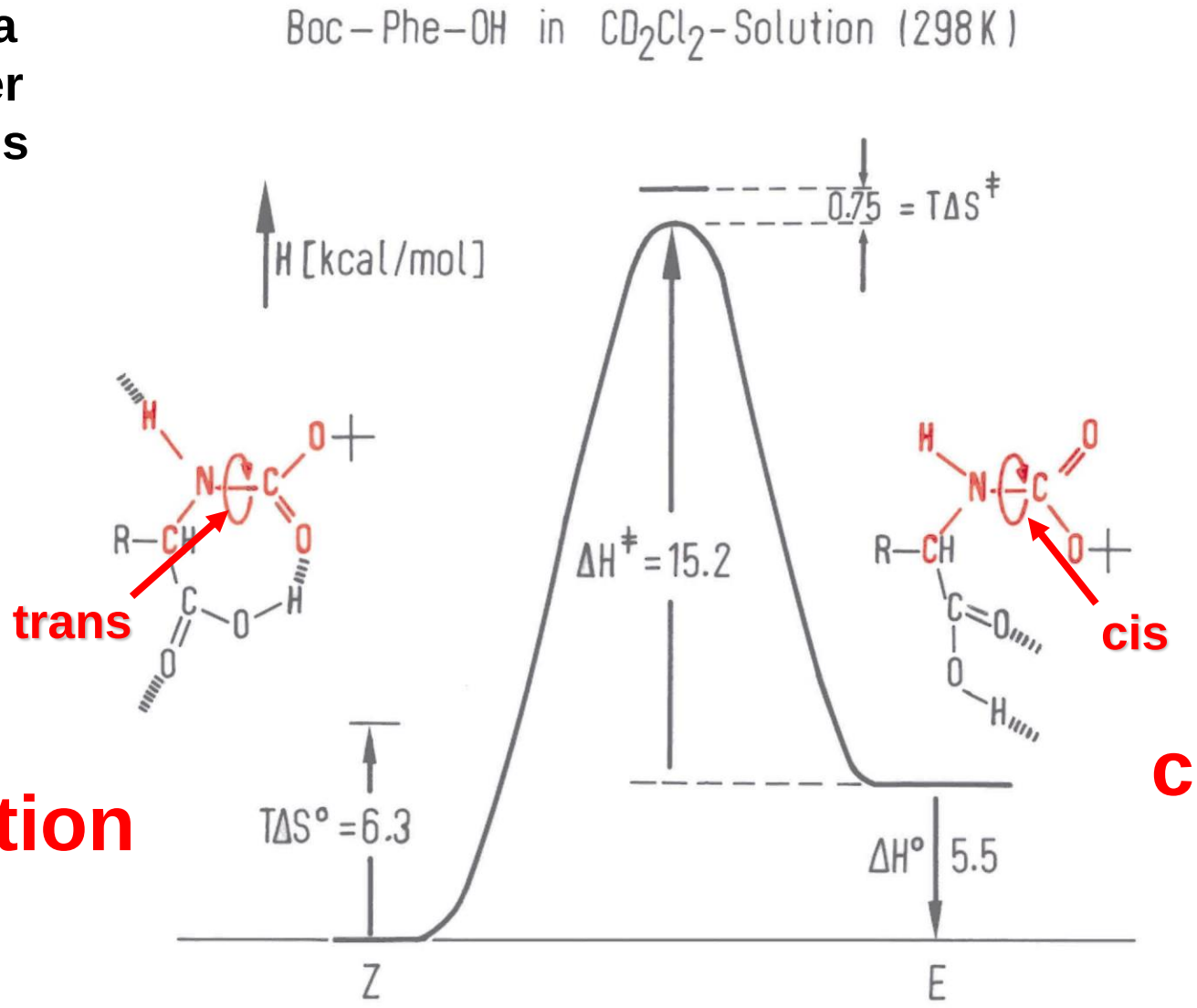
Step 2

Dissolve the crystal at low temperature to avoid interconversion

Step 3

Warm slowly up and observe new signals

G. Zimmermann



solution

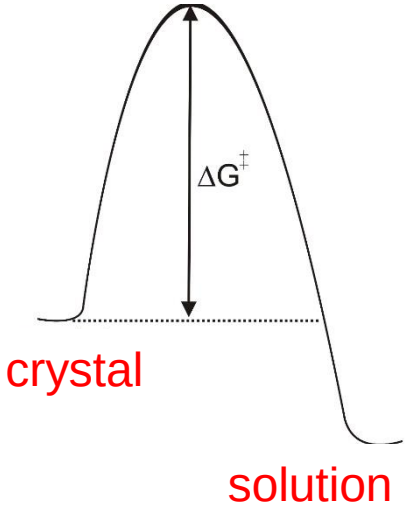
crystal

X-ray structur and solid state NMR

H. Kessler, G. Zimmermann, H. Förster, J. Engel. G. Oepen, W. S. Sheldrick, *ACIE.* **1981,** *20*, 1053-1055.

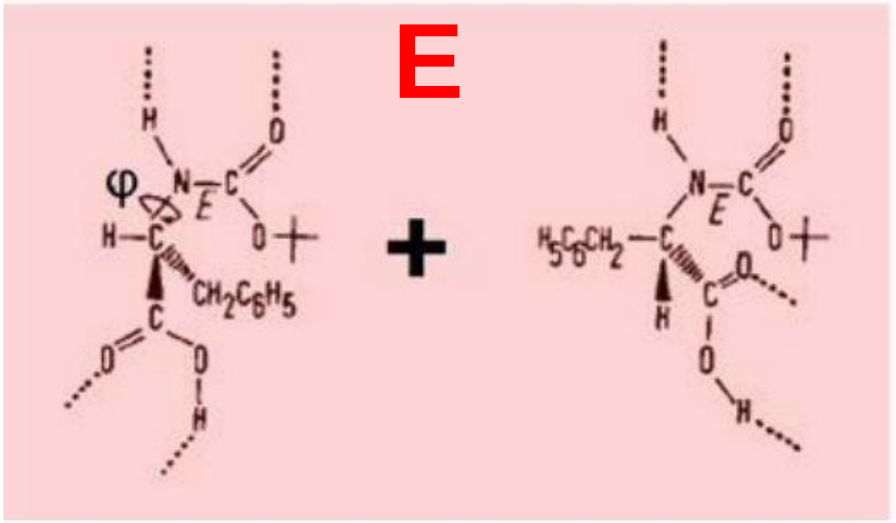
Can the conformation in solution be different from that in the crystal? [1981]

I thought this is **nonsense** and presented two examples in which an unequivocal proof of the difference could be shown

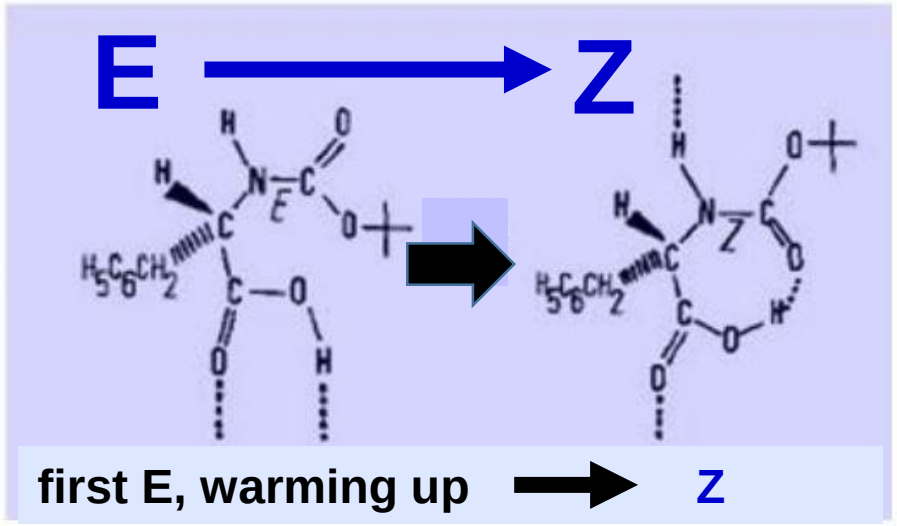


The barrier was selected to be between 10 und 20 kcal

in the crystal

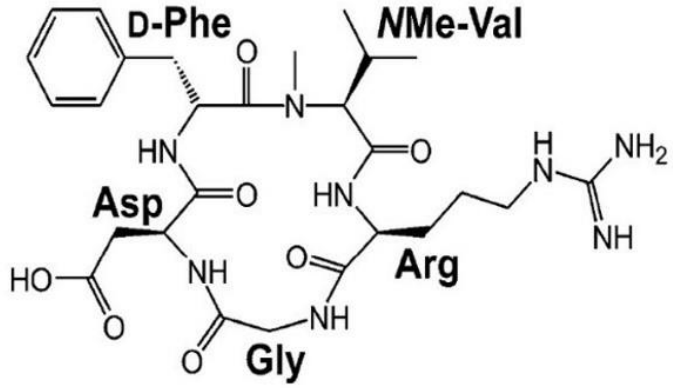


in solution



[H.Kessler et al. *ACIE* **1981**]

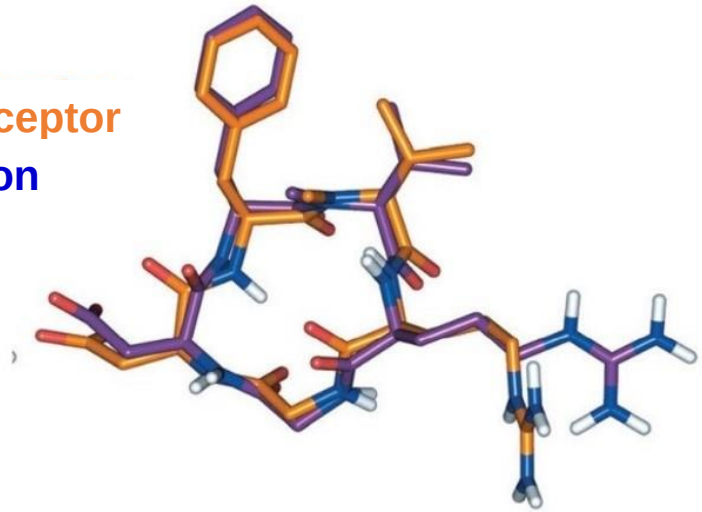
What represents the bioactive conformation better: X-ray or solution structure



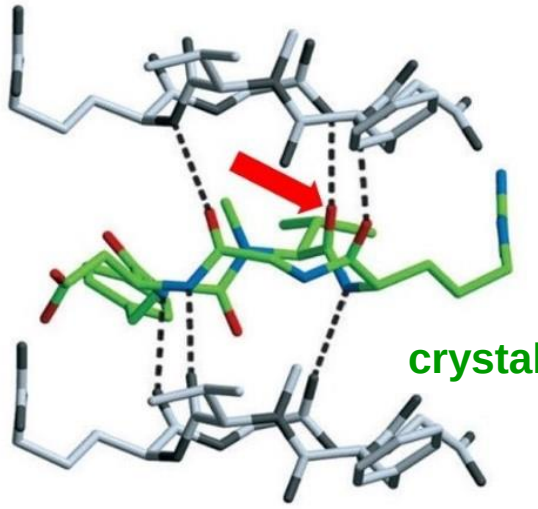
Cilengitid = c(RGDf(*N*Me)V)

[2014]

at the receptor
in solution

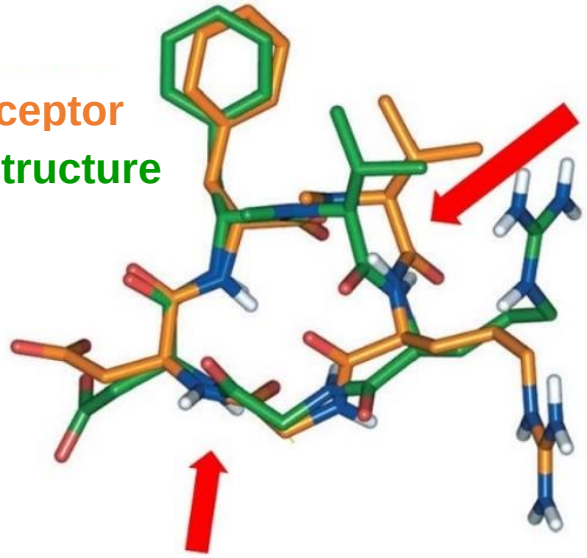


In the crystal the molecules are fixed in the 3D grid



crystal structure

at the receptor
crystal structure

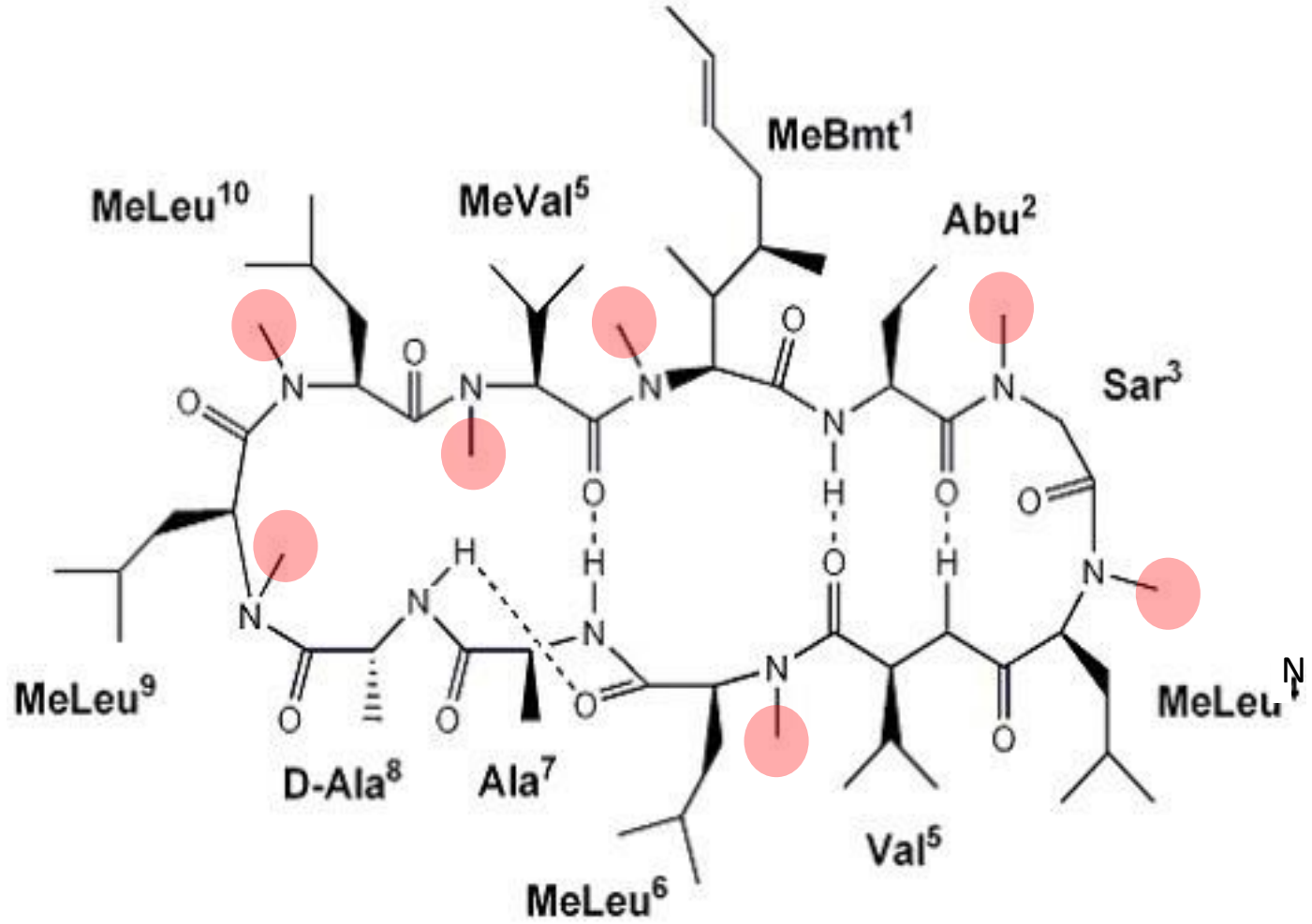


Michael Groll

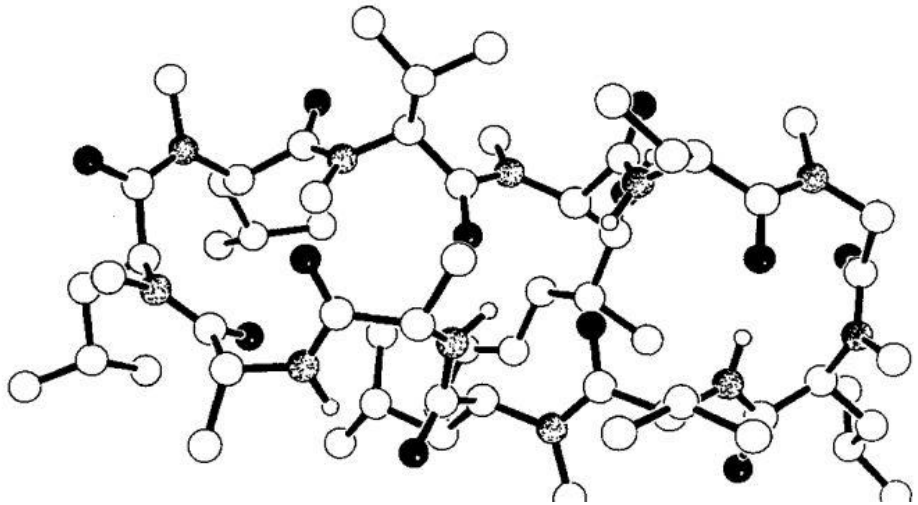
NMR of Cilengitide: M. A. Dechantsreiter et al. J. Med.Chem.1999,42, 3033-3040.
X-ray of isolated Cilengitide: U. Kiran Marelli, A. O. Frank, T. Reiner, B. Wahl, V. La Pietra, E. Novellino, L. Marinelli, M. Groll, H. Kessler, *Chemistry Eur. J*. **2014**, *20*, 14201-14206. **X-ray at the receptor**: J.P. Xiong, T. Stehle, R. Zhang, A. Joachimiak, M. Frech, S.L. Goodman, M. A. Arnaout, *Science* **2002**, *296*, 191-194.

Cyclosporin

7 N-methylations



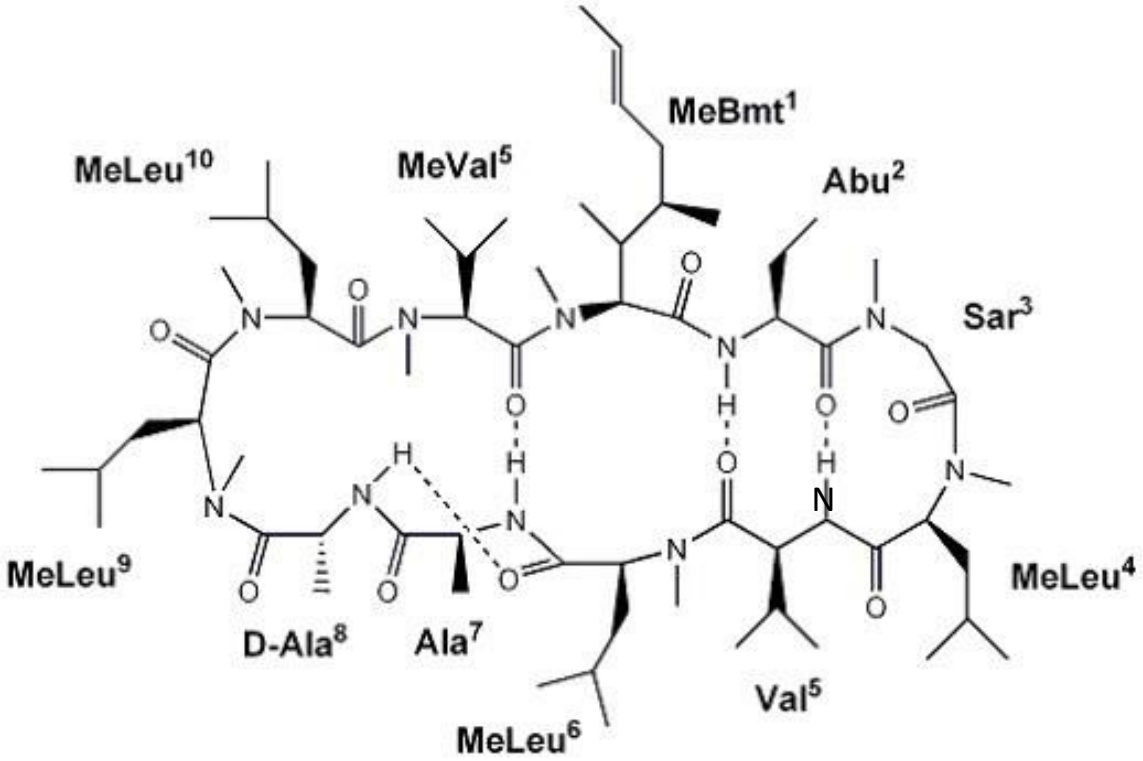
Cyclosporin, the first drug against the rejection of transplanted organs



H. Kessler, H. R. Loosli, H. Oschkinat; *Helv. Chim. Acta* **1985,** *68,* 661-681.

H. R. Loosli, H. Kessler, H. Oschkinat, H. P. Weber, T. J. Petcher, A. Widmer; *Helv. Chim. Acta* **1985,** *68*, 682-704.

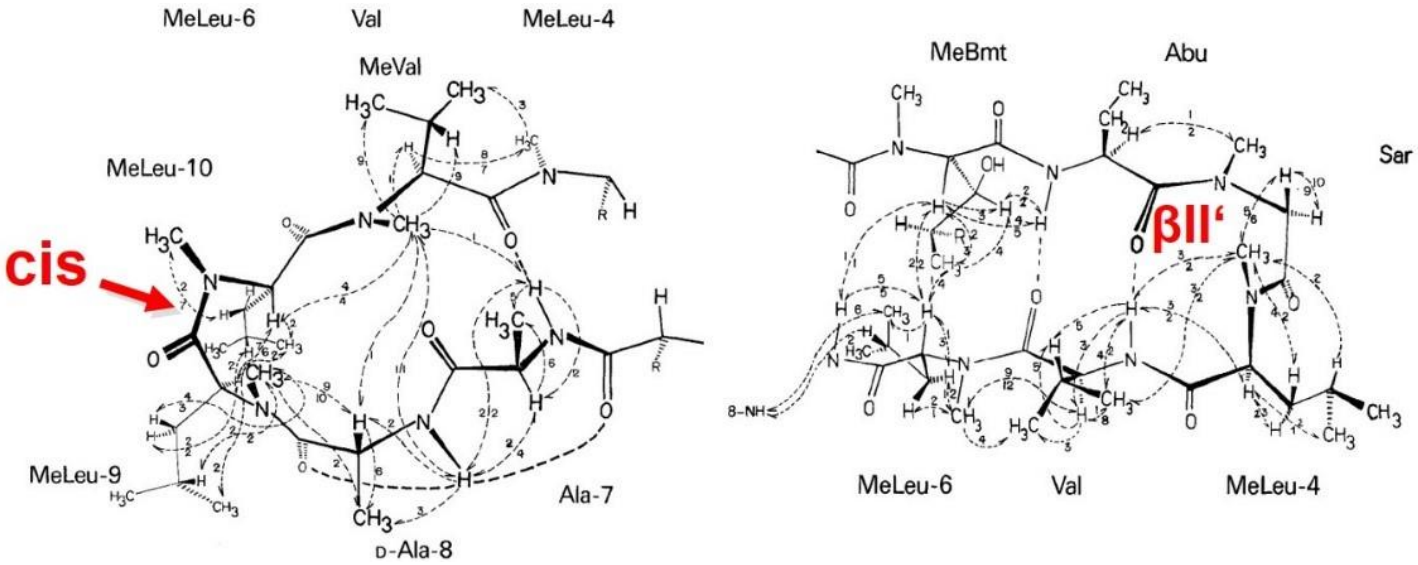
H. Kessler, M. Köck, T. Wein, M. Gehrke; NOESY in $CDCl_3$ *Helv. Chim. Acta* **1990**, *73*, 1818-1832



The first NOE-based conformation

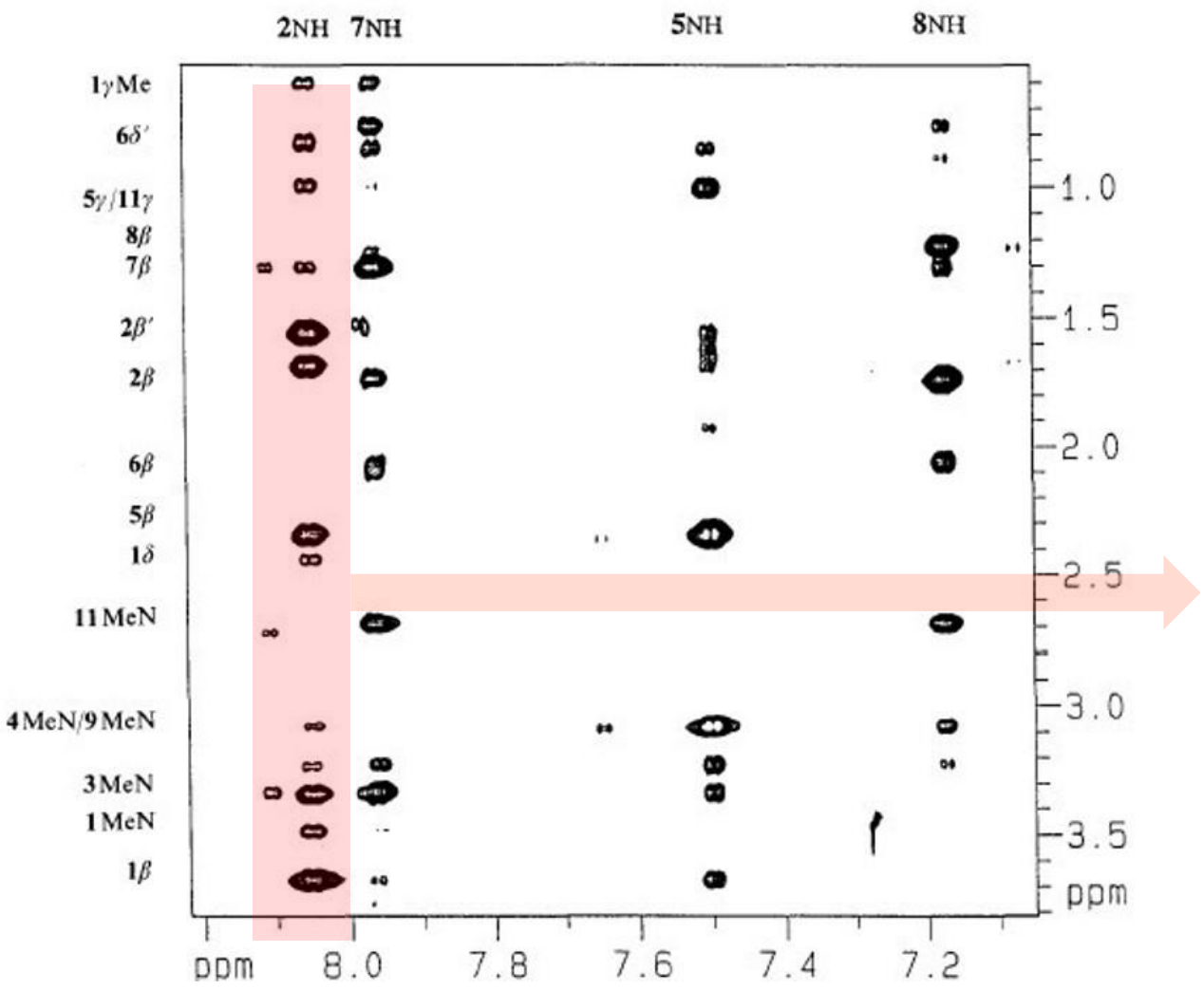
H.-R. Loosli et al. *Helv. Chim. Acta* **1985,** *68*, 668-704. Submitted to *JACS* Febr. 1984, rejected and submitted end of November 1984 to *Helv Chim Acta*)

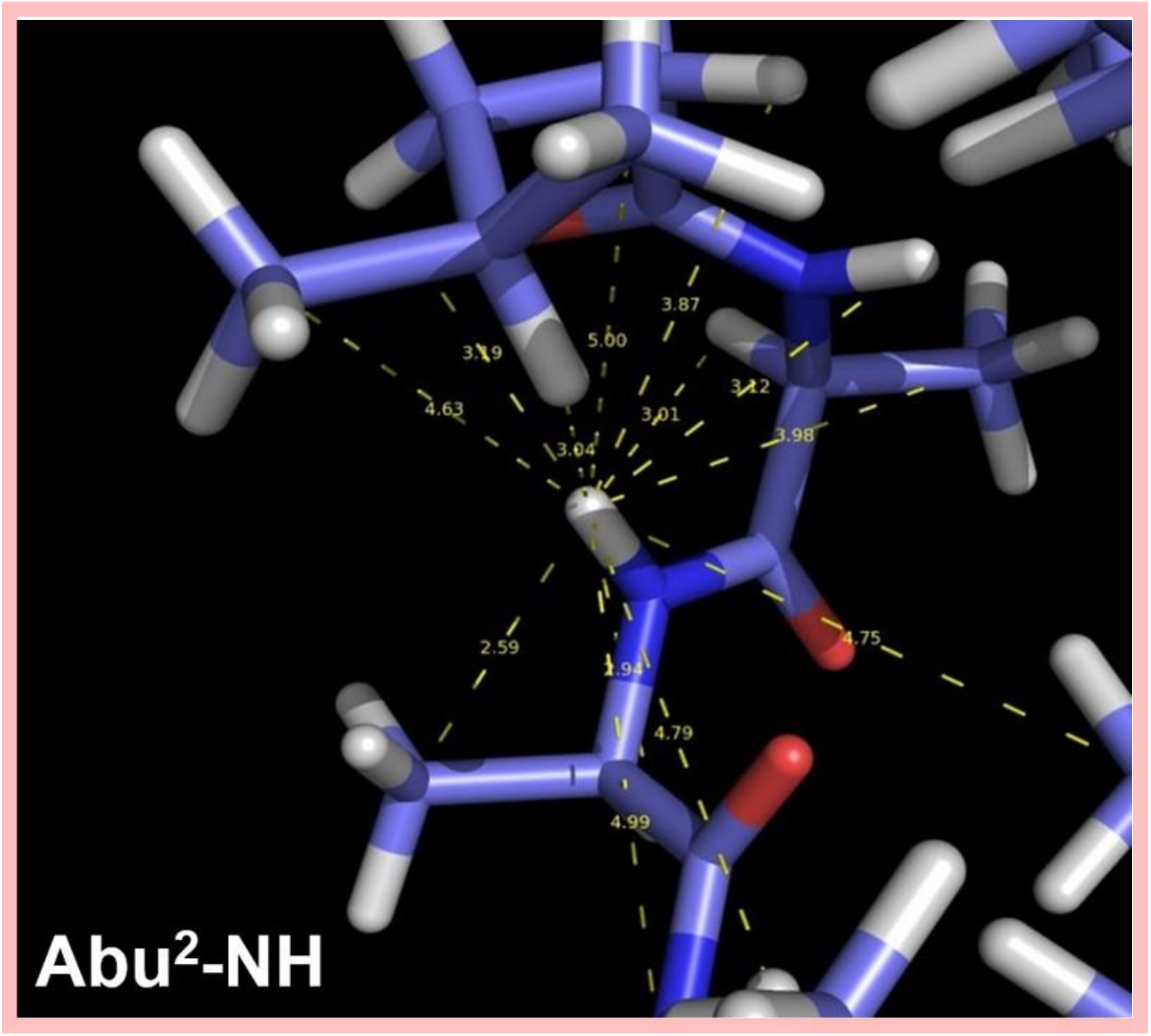
Busi IIA (57 AS) A. Widmer et al. *J. Mol. Biol*. **1985,** *182*, 295-315. submitted August 1984



Later we did NOESY in $CDCl_3$ at lower temperature (250 K, 6 different mixing times):

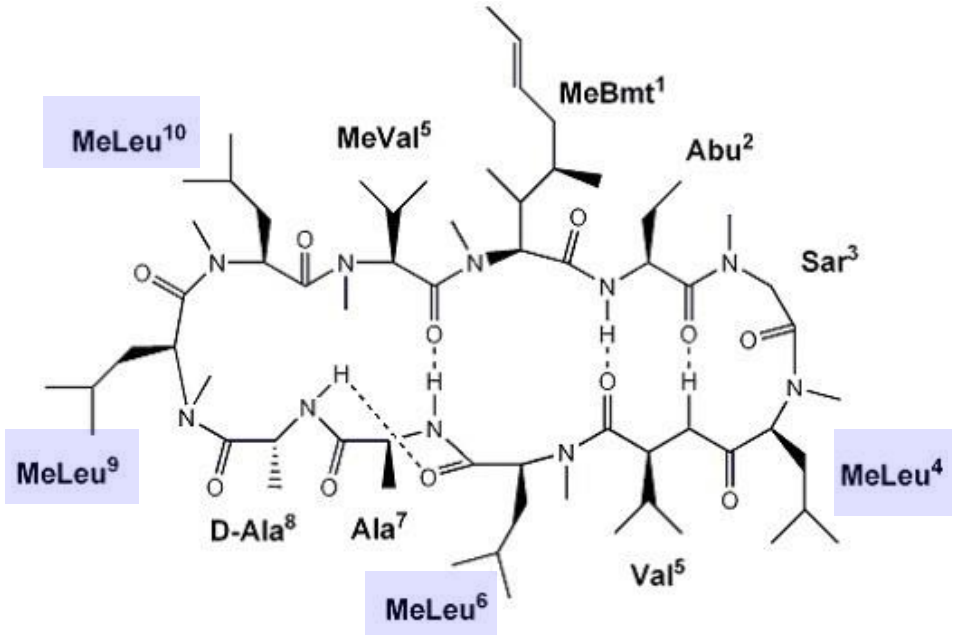
all assignements and structure elements (restraint MD GROMOS) were completely confirmed





NOESY: J. Jeener, B. H. Meier, P. Bachmann, R. R. Ernst *J. Chem. Phys.* **1979**, *71*, 4546–4553.

H. K., M. Köck, T. Wein, M. Gehrke; NOESY in $CDCl_3$ *Helv. Chim. Acta* **1990**, *73*, 1818-1832



Cyclosporin exhibits 16 aliphatic methyl groups

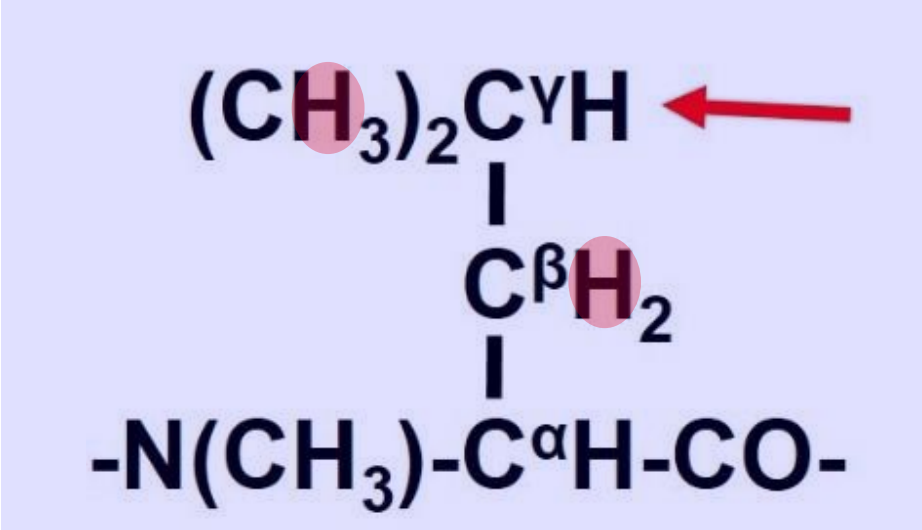
4 x 2 MeLeu	= 8
Val and NMeVal each 2	= 4
+ MeBmt = 3 + Abu =1	= 4

16 aliphatic methyl groups

We need assignment of all methyl groups

Thiocyclosporin (exhibited 2 conformations)

[with D. Seebach, ETH] = **32 methyl signals**

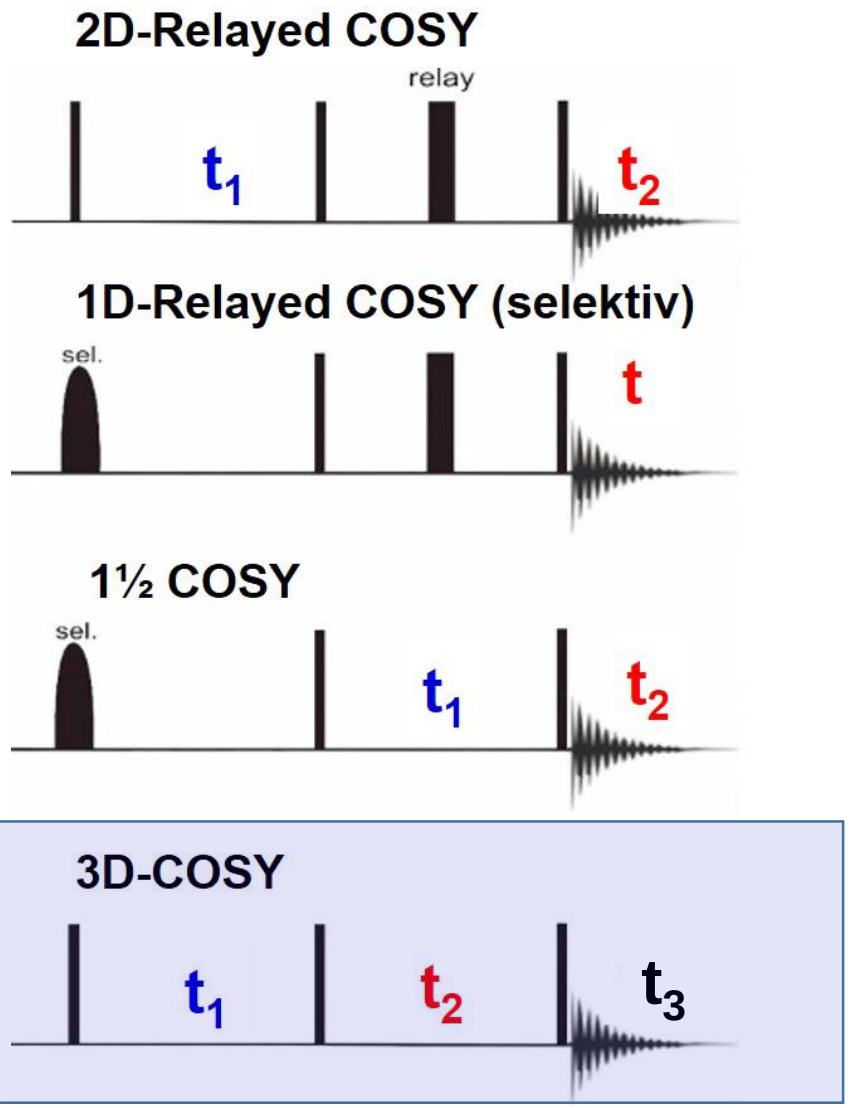


each methine proton couples to 8 vicinal neighbors resulting in four overlapping broad multiplets (each 8 x 7 = 56 Hz)

The solution of the problem: relayed techniques

H. Kessler, H. R. Loosli, H. Oschkinat;; *Helv. Chim. Acta* **1985,** *68,* 661-681. (Later HQQC (hetero 3D) with methyl selection)

Hiking between dimensions: selective excitation



H. Kessler., H. Oschkinat, C. Griesinger, W. Bermel, *J. Magn. Reson*. **1986**, *70*, 106-133.

C. Griesinger, O.W.Sørensen, R.R. Ernst, *JACS* **1987**, *109*. 7227-7228.

H. Kessler, U. Anders, G. Gemmecker, S. Steuernagel, *J. Magn. Reson*. **1989**, *85*, 1-14.

The First Heteronuclear 3D Spectrum

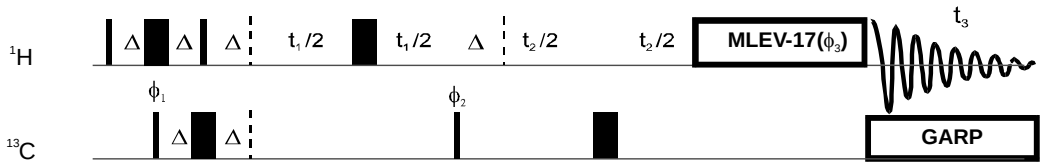
December **1989** Honorary Degree for Tony Keller (TU Berlin)
Richard Ernst presented the homonuclear 3D NMR.

Dieter Ziessow

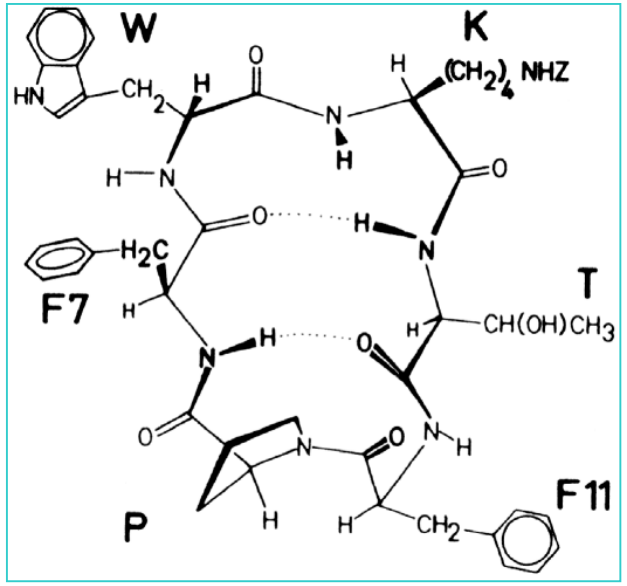
Dr. h.c.

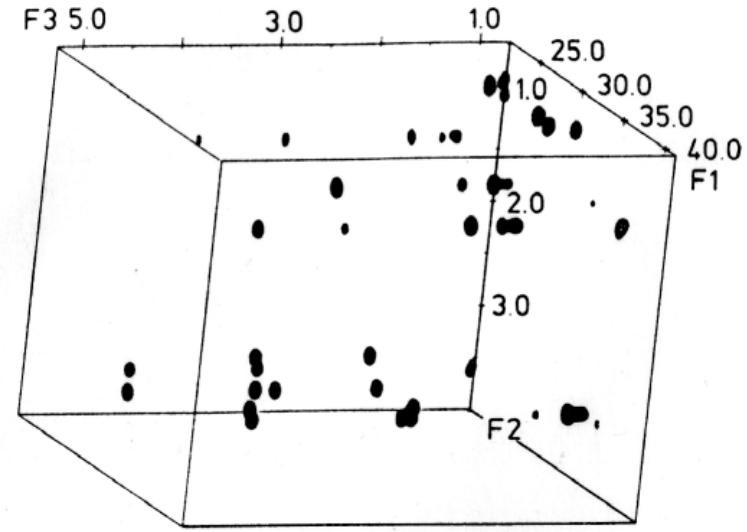
He pointed out that it makes no sense to do it with ^{13}C as the spectral width requires too many acquisitions.

However: 3D-DEPT-TOCSY (selective excitation of CH_2 groups)



The Veber-Hirschmann-Peptide





P. Schmieder

H. Oschkinat

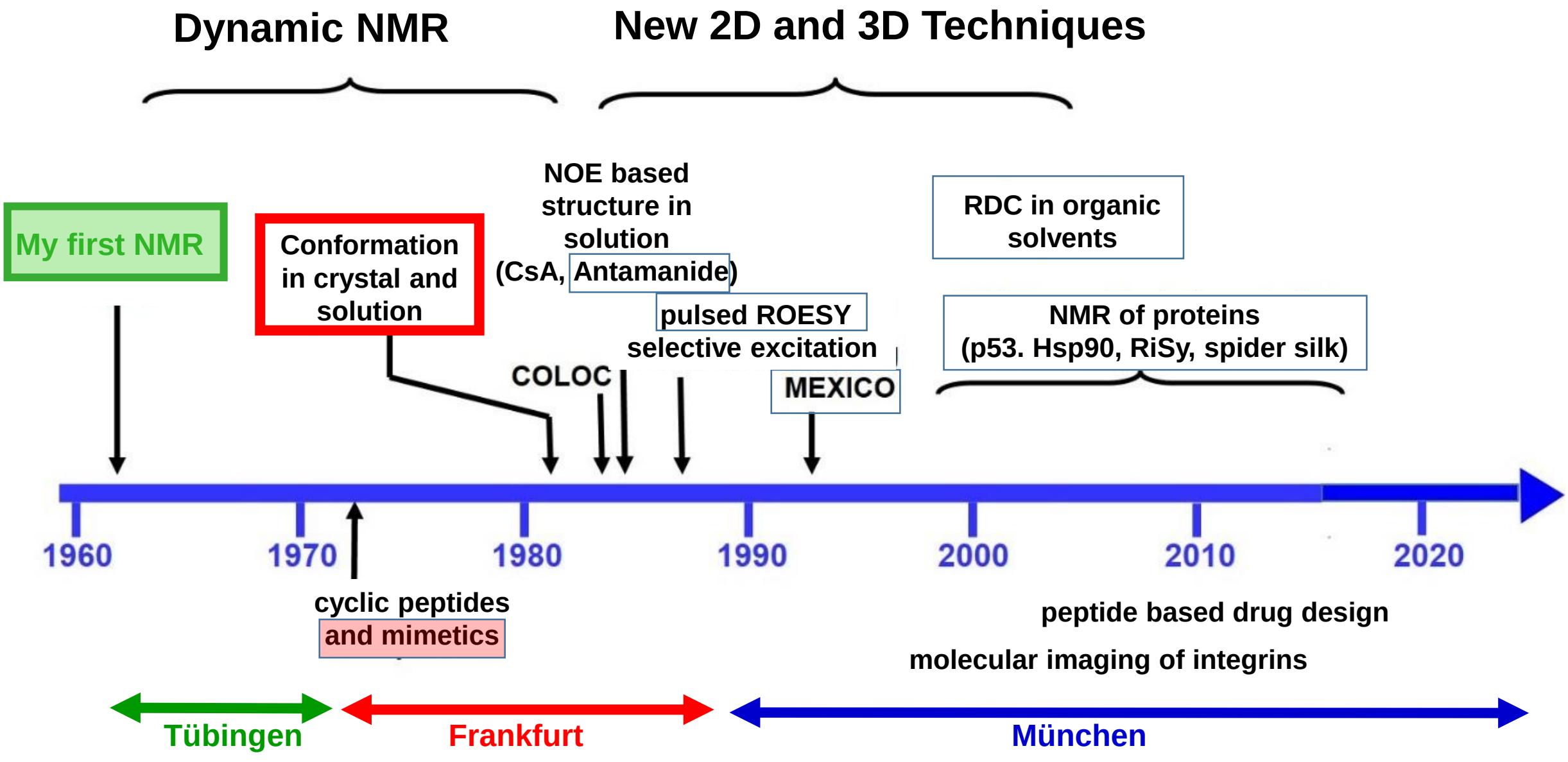
Reduced ^{13}C-spectral width by selective excitation of CH_2-groups using DEPT-(90)

C. Griesinger, O.W.Sørensen, R.R. Ernst, *JACS* **1987**, *109*. 7227-7228

P. Schmieder, H. Kessler, H. Oschkinat; ACIE **1990**, *29*, 546-548. **only 14 citations!**

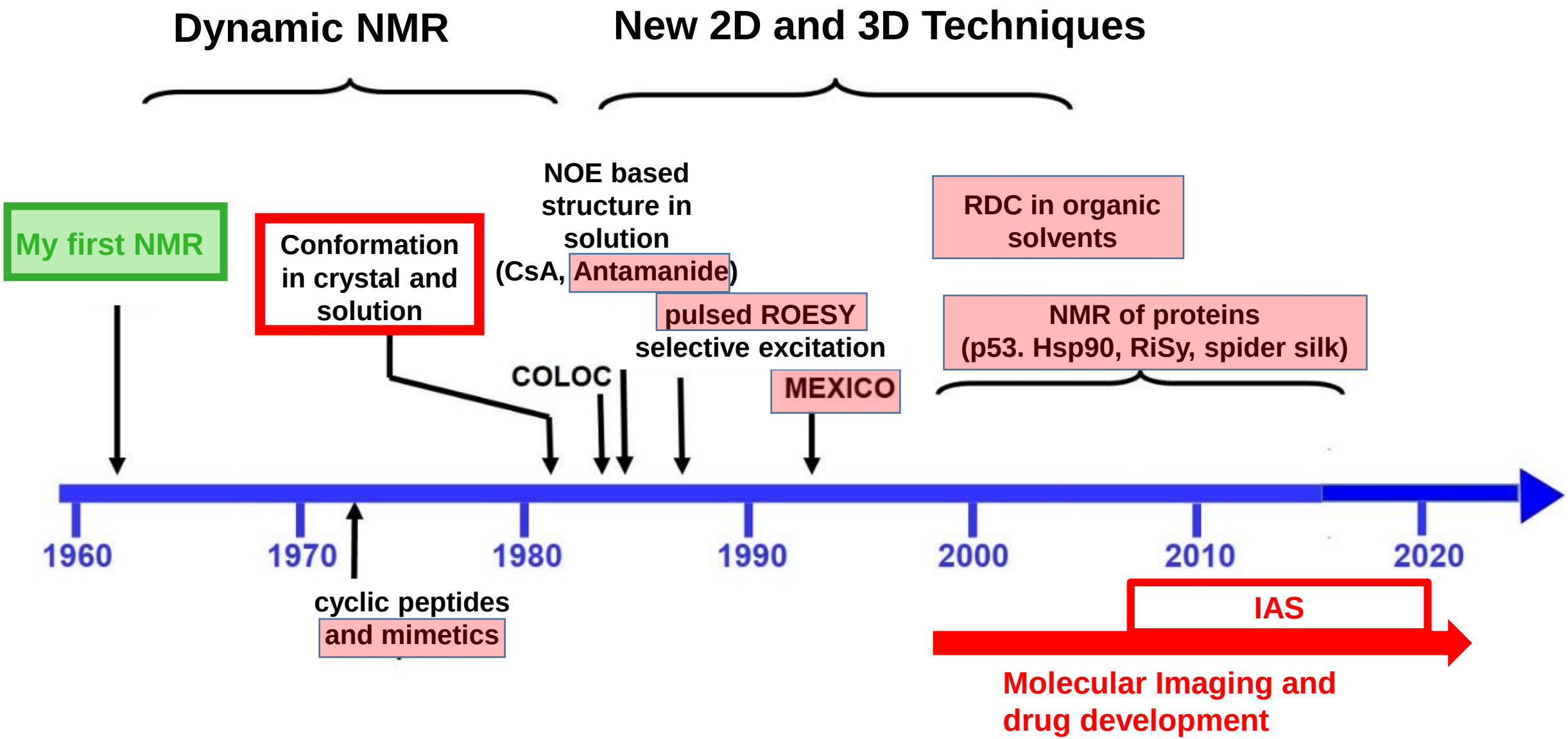
Later we used it for more complex systems such as the Thio-Cyclosporins

My contributions to NMR

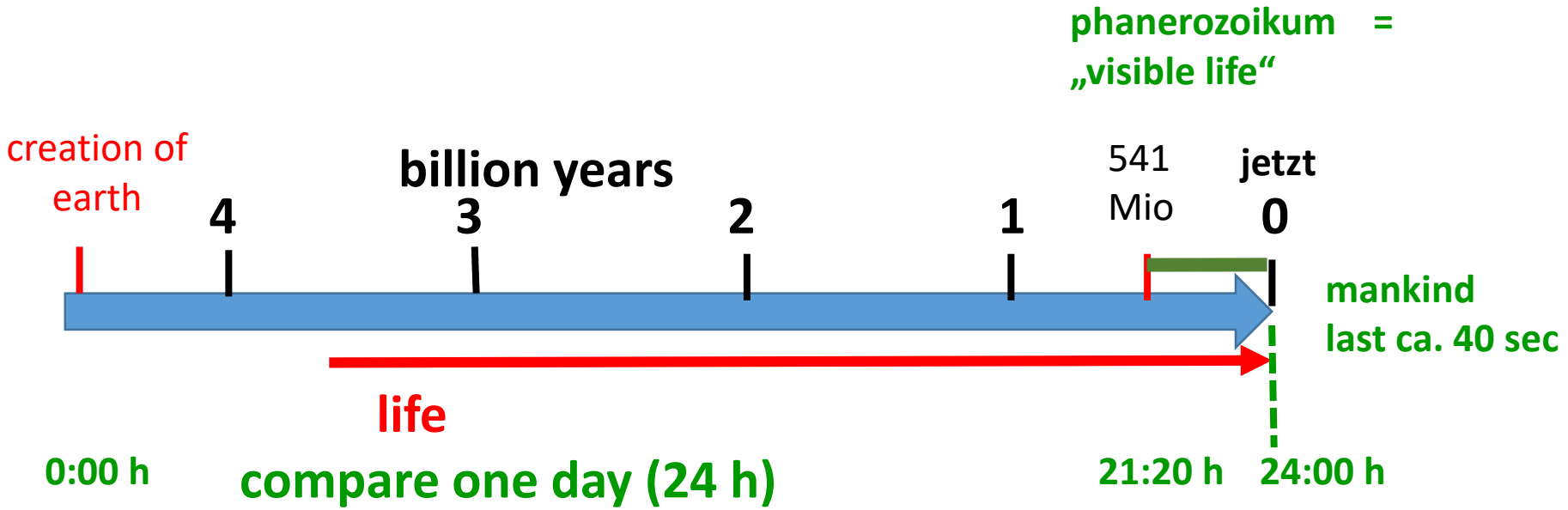


My contributions to NMR

here not discussed



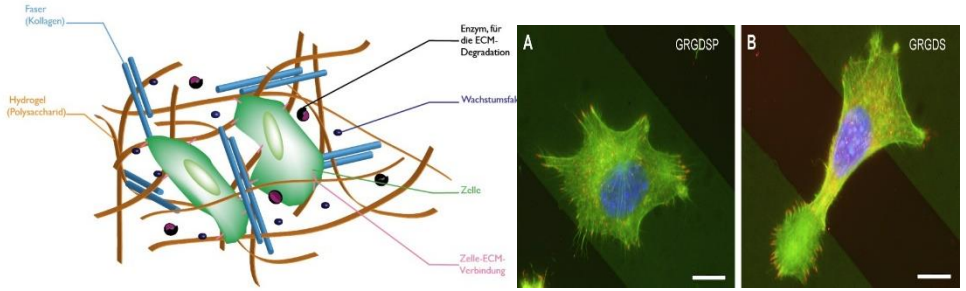
Cell adhesion is essentail for the development of higher life



The Venus of Hohle-Fels (Schwäbische Alb, ca. 35000 Jahre alt) was created in the last second

Hihger life needs not only communication between cells but

- recognition of surrounding (but this was already discovered: *quorum sensing*),
- **targeted migration,**
- **apoptosis,**
- signals for proliferation

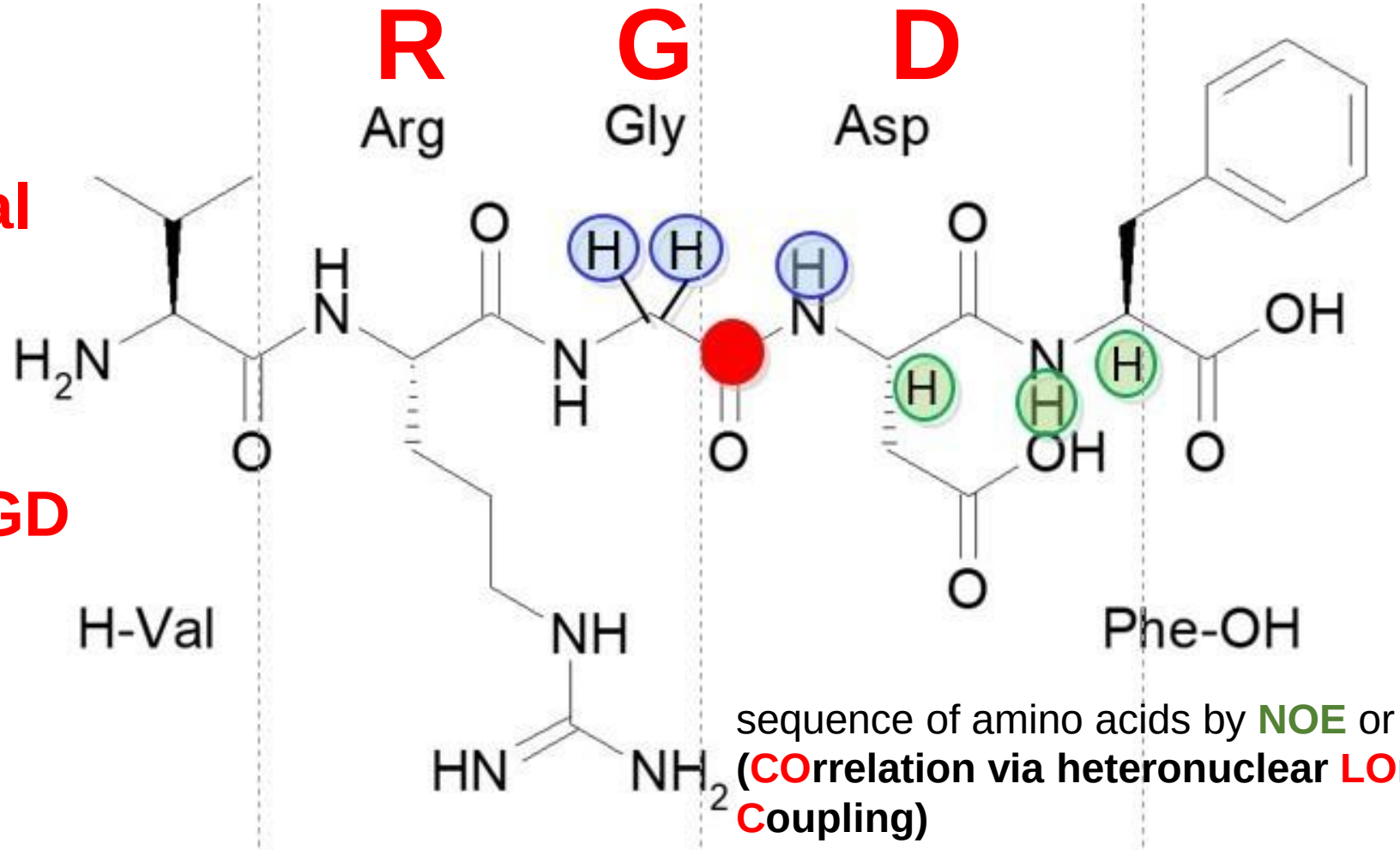


Why needs nature such a long time for the development of multicellular life?

RGD, the important motive for cell adhesion (Ruoslahti und Pirschbacher, 1979)

24 mammalial integrins

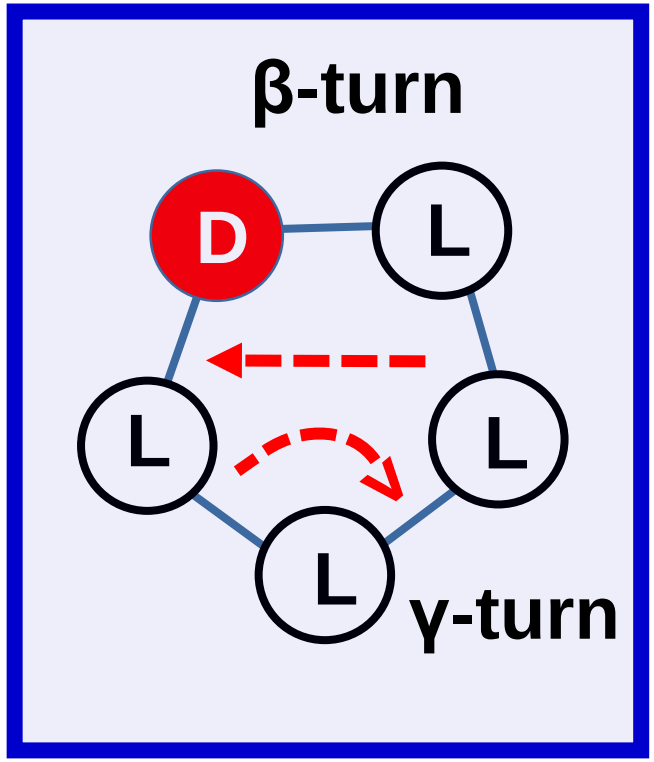
8 of them recognize RGD



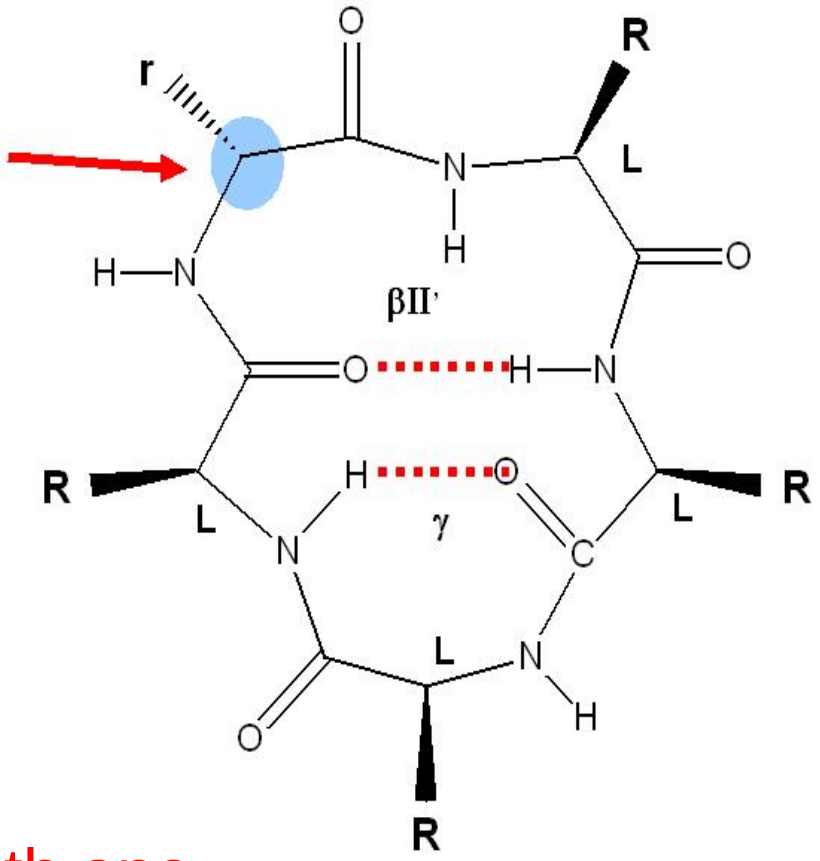
sequence of amino acids by **NOE** or **COLOC** **(COrrelation via heteronuclear LOng range Coupling)**

Integrins, the cell adhesion molecules, bind to the extracellular matrix (e.g. via RGD). information through the cell membranes. **Their expression is regulated by the Mikro-RNAs** (Nobel Prize in Medicine 2024 Ambros, Ruvkun).

To explore the conformation of RGD for different integrins we used template of five (or six) amino acids in a cyclus



D-Aminosäure



The *canonical structure* of this pentapeptide with one D-amino acid is independent from the nature of R

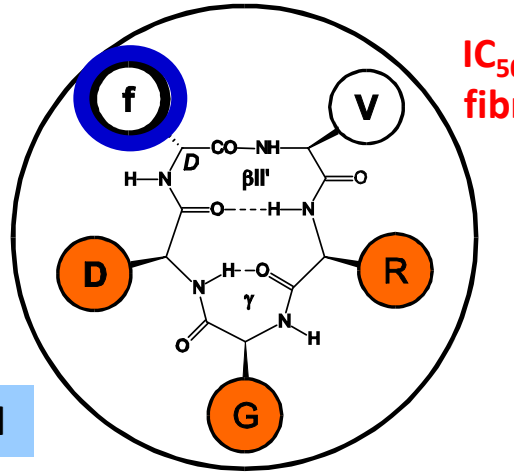
Y. A. Bara, A. Friedrich, H. K., M. Molter; *Chem. Ber.* **1978,** *111*, 1045-1057; H. Kessler, H. Kogler; *Liebigs Ann. Chem.* **1983**, 316-329; H. K., B. Kutscher; *Tetrahedron Lett*. **1985**, *26*, 177-180.

Spatial screening: D-Amino Acid Scan of cyclo(-VRGDF-)

linear reference GRGDSPK: 1.2 mmol

also for αIIbβ3

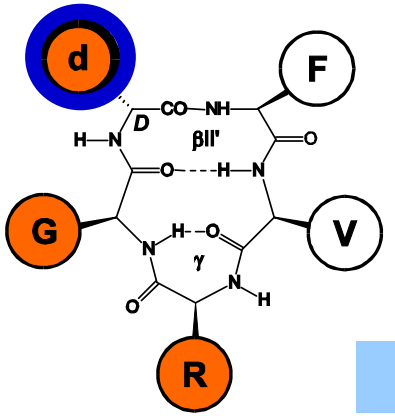
super-activ



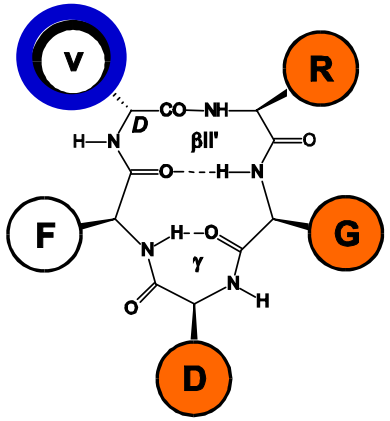
0.002 µmol

IC_{50} (αIIbβ3) against fibrinogen >10µmol

selective

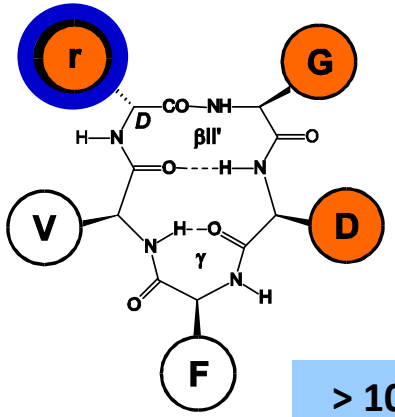


> 10 µmol

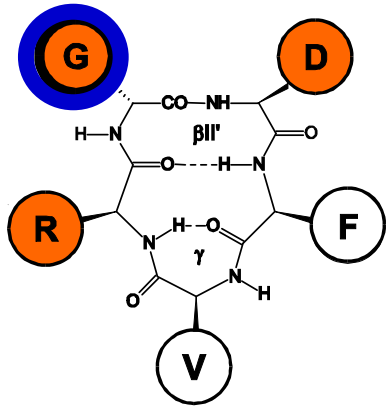


0.011 µmol

IC 50 (αvβ3 against vitronectin)



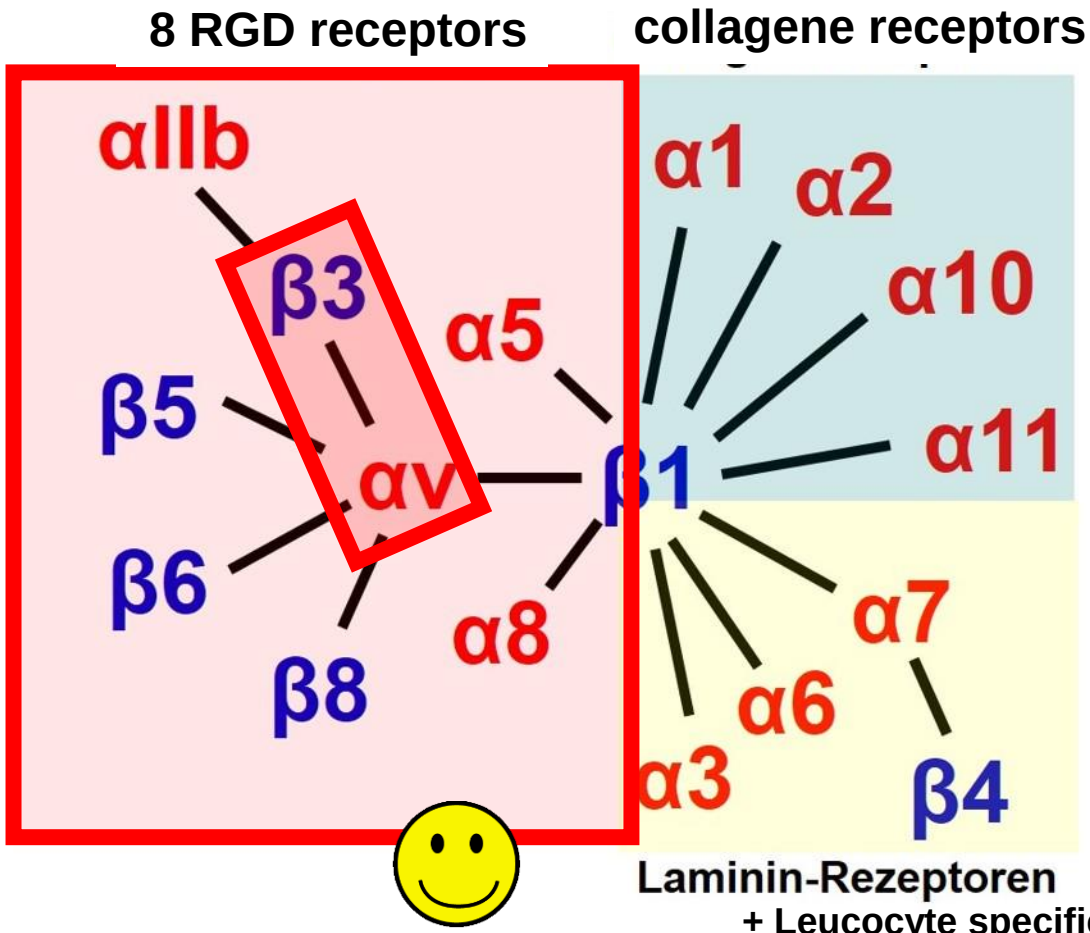
> 10 µmol



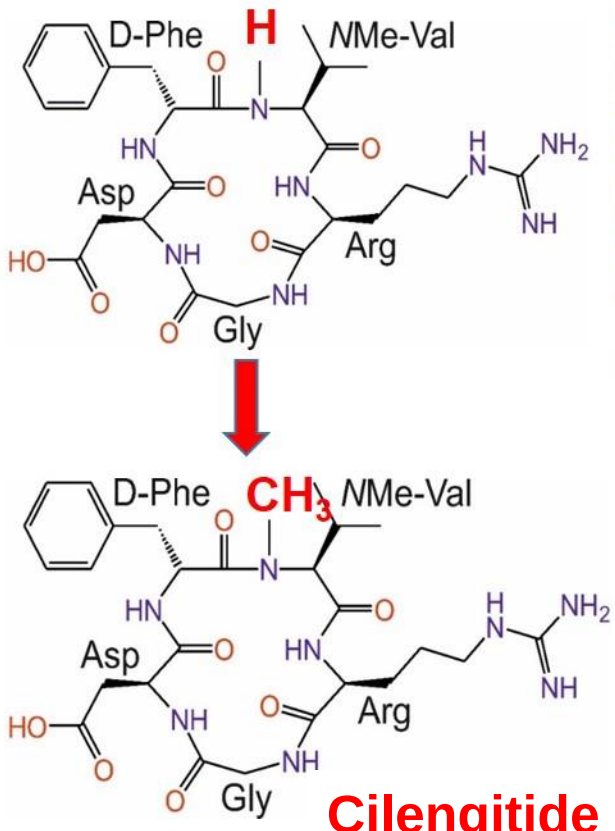
0.15 µmol

M. Aumailley, M. Gurrath, G. Müller, J. Calvete, R. Timpl, H. Kessler, *FEBS Lett*. **1991**, *291*, 50-54.

Cilengitide



„stem peptide“



Gerhard Müller und Marion Gurrath

Michael Dechantsreiter

αvβ3 = 0,6 nM

αvβ5 = 8,4 nM

αvβ6 = 2050 nM

αvβ8 = 2350 nM

α5β1 = 14,9 nM

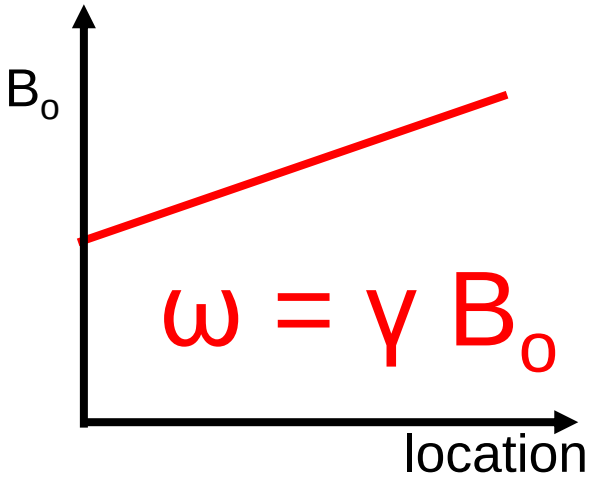
αIIbβ3 = 5400 nM

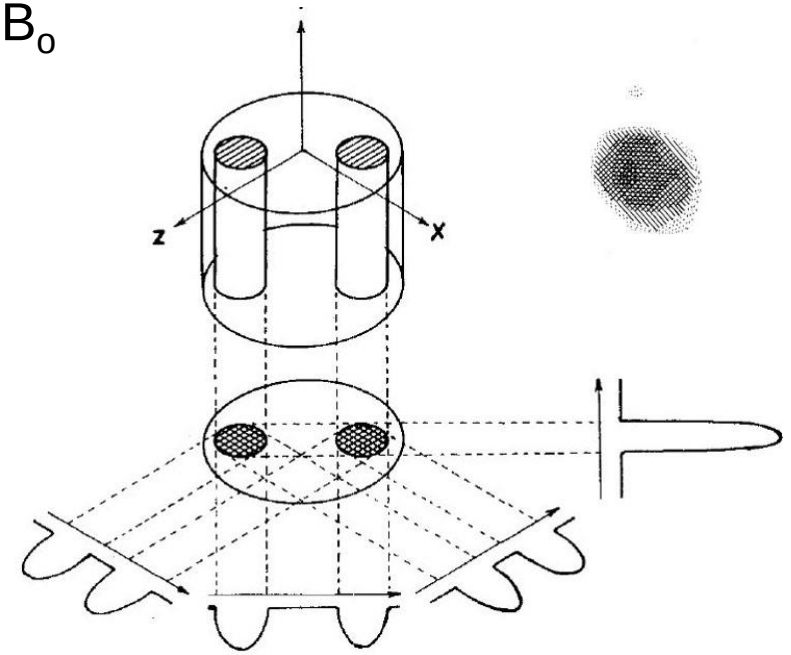
M. A. Dechantsreiter, E. Planker, B. Mathä, E. Lohof, G. Hölzemann, A. Jonczyk, S. L. Goodman, H. Kessler, *J. Med. Chem*. **1999**, *42*, 3033-3040.

Imaging by NMR

1974 Kandersteg-Konferenz „Magnetresonanz in biologischen Systemen“ organised by Swiss NMR reseachers (Wüthrich, Seelig, Ernst ..) [R.R.Ernst, Autobiografie, 2020, p. 135-137]

The signal of water appears at its characteristic frequency, which is determined by B_o





Lauterbur presented „Zeugmatography“

Ernst Fourier Zeugmato-graphy

NMR = Nuclear Magnetic Resonance

~~Nuclear~~ Magnetic Resonance-Imaging (MRI) or MRT

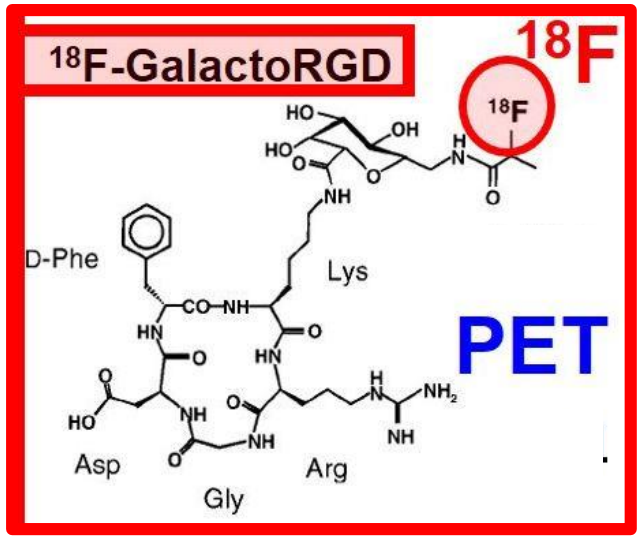
P.C.Lauterbur: Image Formation by Induced Local Interactions: Examples Employing NMR. *Nature* 1973, *242*, 190-191.

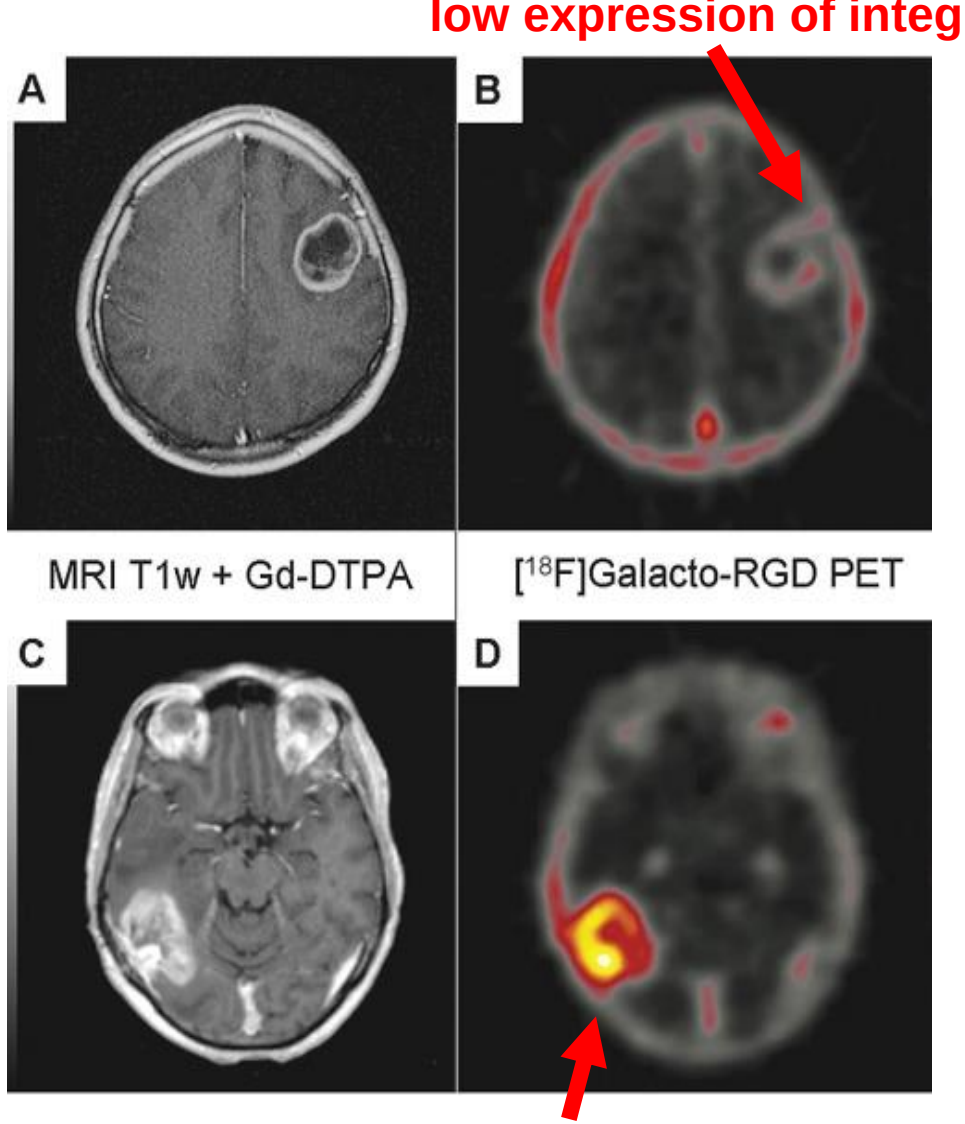
When Lauterbur first submitted his paper with his discoveries to *Nature*, the paper was rejected by the editors of the journal. Lauterbur persisted and requested them to review it again, upon which time it was published and is now acknowledged as a classic *Nature* paper. The *Nature* editors pointed out that the pictures accompanying the paper were too fuzzy, although they were the first images to show the difference between heavy water and ordinary water. Lauterbur said of the initial rejection: 'You could write the entire history of science in the last 50 years in terms of papers rejected by *Science* or *Nature*' (Wikipedia article on Paul Lauterbur, accessed 03-08-2012). R.R. Ernst, NMR Fourier Zeugmatography *J.Magn. Res*. **2011**, *213*, 510-512.

Imaging of glyoblastoma multiform,
the most aggressive brain tumor.

Enhanced contrast by paramagnetic Gadolinium (Gd)
The tumor has a different relaxation time and is already easily detectable..
Both tumors have different expression of integrins as have been proven by our highly specific ligand „^{18}F-Galacto-RGD“ in positron emission tomography (PET).

Molecular Imaging allows to detection and differentiation of cancer subtypes in animals and man





O. Schnell, B. Krebs, J. Carlsen, I. Stangier, C. Goetz, R. H. Goldbrunner, H.-J. Wester, R. Haubner, G. Pöpperl, M. Holtmannspötter, H. Kessler, J.-C. Tonn, M. Schwaiger, A. J. Beer, Imaging of Integrin $\alpha_v\beta_3$ Expression in Patients with Malignant Glioma by [^{18}F]Galacto-RGD PET, *Neuro-Oncology*, 2009, *11*, 861-870.

The **mikro-RNA let-7** gene codes the expression of the β3-integrina subtype.
Its absense leads e.g. to melanoma (with high expression of integrin **αvβ3**) .

It regulated the melanoma cell survival and metastasis formation

The idea to study this topic was inspired by NMR and conformational studies of cyclic peptides.

Meanwhile we achieved to address five of the eight RGD-reconizing integrin subtypes by small molecules with very high affinity and selectivities.

It is used for Molecular Imaging or therapy = Theranostics (substitution of positron emitter ^{68}Ga by the α-emitter ^{177}Lu

NMR is the most important technology for chemistry

structure

constitution (connectivities within the molecule)
configuration (stereostructur)

dynamics

dynamics (intramolecular mobility)

intermolecular interactions

interaction with other molecules (e.g. exact drug – receptor)

Every chemical lab has ist own NMR spectometer

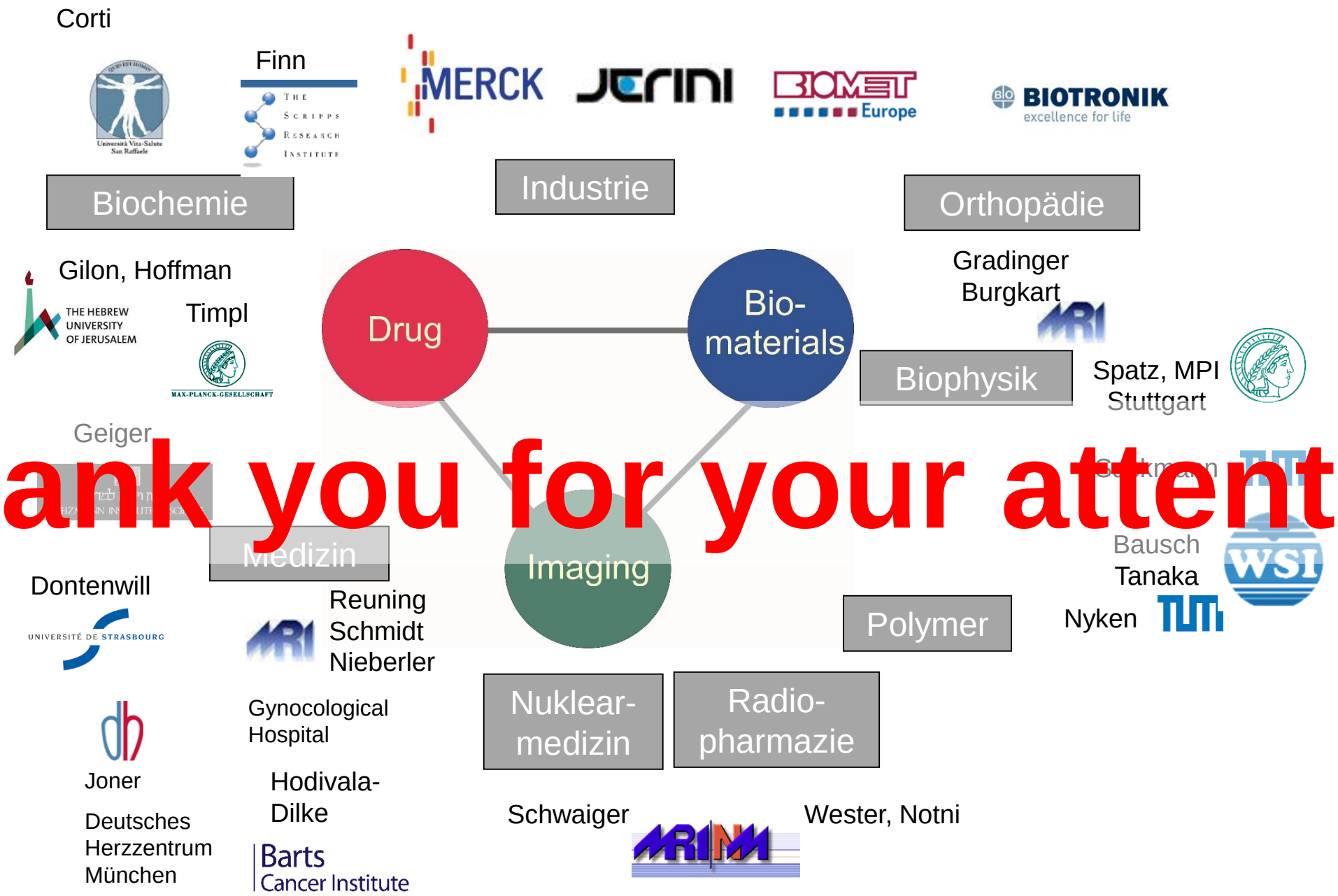
Many thanks to all my coworkers

(160 Ph.D. students and many post-docs (21 of the are professors))

and cooperation partners

(a large number in the interdisciplinary work

Interdisziplinarität im RGD Gebiet



Thank you for your attention