



SOLID-STATE NMR

&

POLYMORPHISM

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- **NMR relies on local environment rather than long-range order**
- **Works well on microcrystalline “powder” samples**
- **Produces immediate information on the asymmetric unit
(intra/intermolecular)**
- **Can yield internuclear distances
(intra/intermolecular)**
- **Can be used in conjunction with powder XRD to yield total
crystal structures**
- **Can readily distinguish polymorphs
(and monitor transformations)**
- **Can be used for heterogeneous systems
(formulated drugs)**

N.B. Can also be used for amorphous systems

FUNDAMENTALS
of
SOLID-STATE NMR

ANISOTROPIC NUCLEAR MAGNETIC INTERACTIONS

- | | isotropic value |
|--|--|
| • SHIELDING | σ (\rightarrow “chemical shift”) |
| • INDIRECT (“SCALAR”) COUPLING | J (“coupling constant”) |
| • DIPOLAR COUPLING | 0 |
| • QUADRUPOLEAR COUPLING
(for $I > \frac{1}{2}$ only) | 0 |
-
- ▶ These are all **TENSOR** properties.
 - ▶ Each of these can be specified by 3 **PRINCIPAL COMPONENTS**, plus three angles to specify the orientation in B_0 .
 - ▶ In each case, the interaction energy depends on $(3 \cos^2 \theta - 1)$, where θ is the angle between B_0 and an appropriate molecule-fixed direction.
 - ▶ In solution, $\langle 3 \cos^2 \theta - 1 \rangle \rightarrow 0$, so effects of anisotropy vanish.

HIGH-RESOLUTION SOLID-STATE NMR

*For direct observation of a dilute-spin nuclide (such as ^{13}C)
In the presence of an abundant-spin nuclide (such as ^1H)*

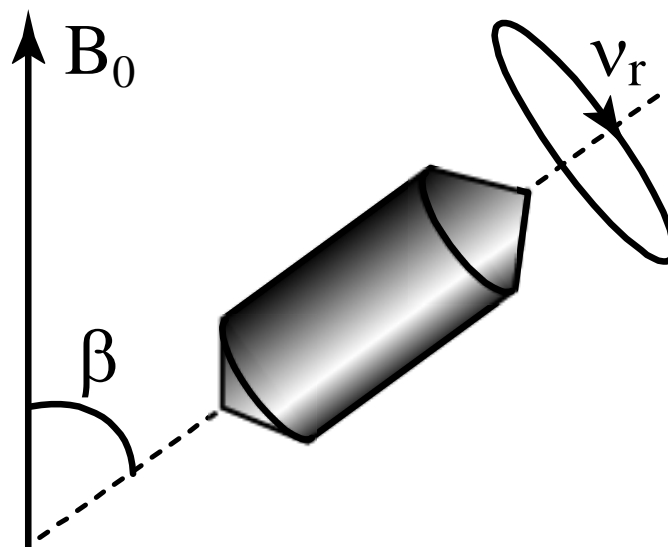
THE PROBLEMS

THE TECHNIQUES

1	STRONG DIPOLAR INTERACTIONS	HIGH-POWER DECOUPLING
2	LONG SPIN-LATTICE RELAXATION TIMES	CROSS-POLARIZATION
3	SHIELDING ANISOTROPY	RAPID MAGIC-ANGLE ROTATION

—————→ **CPMAS NMR**

MAGIC-ANGLE SPINNING (MAS)

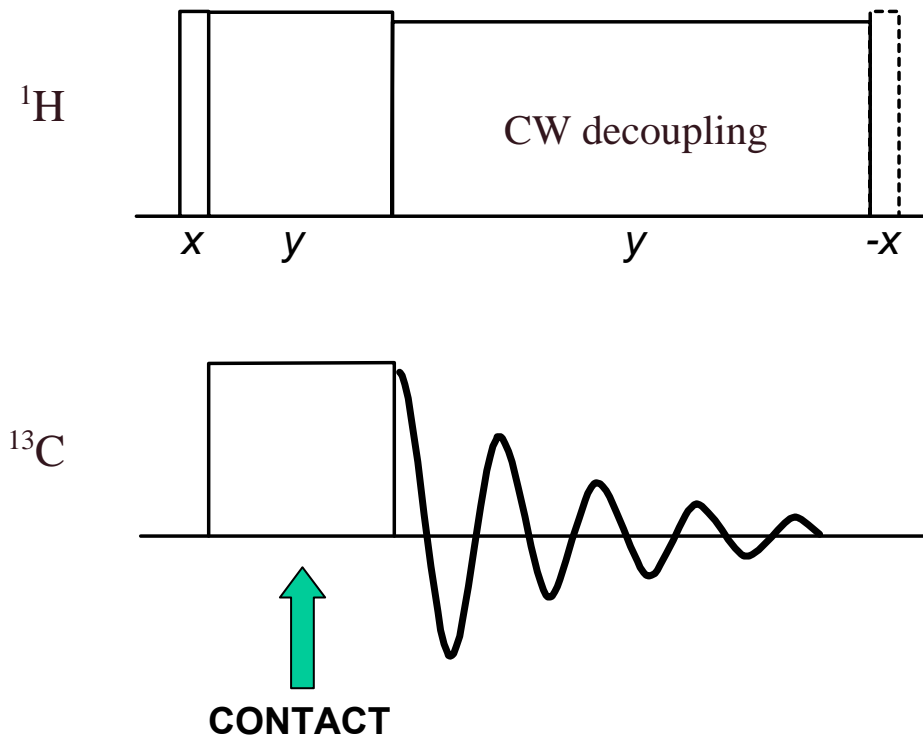


$\beta = 54.7^\circ$

SPIN RATES up to 35 kHz

Rotor diameters 2.5 to 7.5 mm

CROSS-POLARISATION PULSE SEQUENCE



Hartmann-Hahn matching condition: $\gamma_{\text{H}} \mathbf{B}_{1\text{H}} = \gamma_{\text{C}} \mathbf{B}_{1\text{C}}$

Contact time: 1-10 ms

Gain in S/N: $\gamma_{\text{H}} / \gamma_{\text{C}} \sim 4$

Recycle delay $\sim 5 \times T_1$ (^1H) – leads to further gain in S/N

PROTON RELAXATION for SOLIDS

T_1 SPIN-LATTICE RELAXATION **~ s to hours**

— governs recycle delay

$T_{1\rho}$ SPIN-LATTICE RELAXATION IN THE ROTATING FRAME **~ tens of ms**

— governs decay of ^{13}C magnetization at long contact times

T_2 TRANSVERSE RELAXATION TIME **~ tens of μs for static samples**

— governs linewidth

ALSO:

T_{CP} CROSS POLARIZATION TIME

— governs rise of ^{13}C magnetisation at short contact times

**For HOMOGENEOUS SAMPLES T_1^{H} is AVERAGED to the SAME VALUE
for ALL PROTONS by SPIN DIFFUSION**

— similarly for $T_{1\rho}^{\text{H}}$

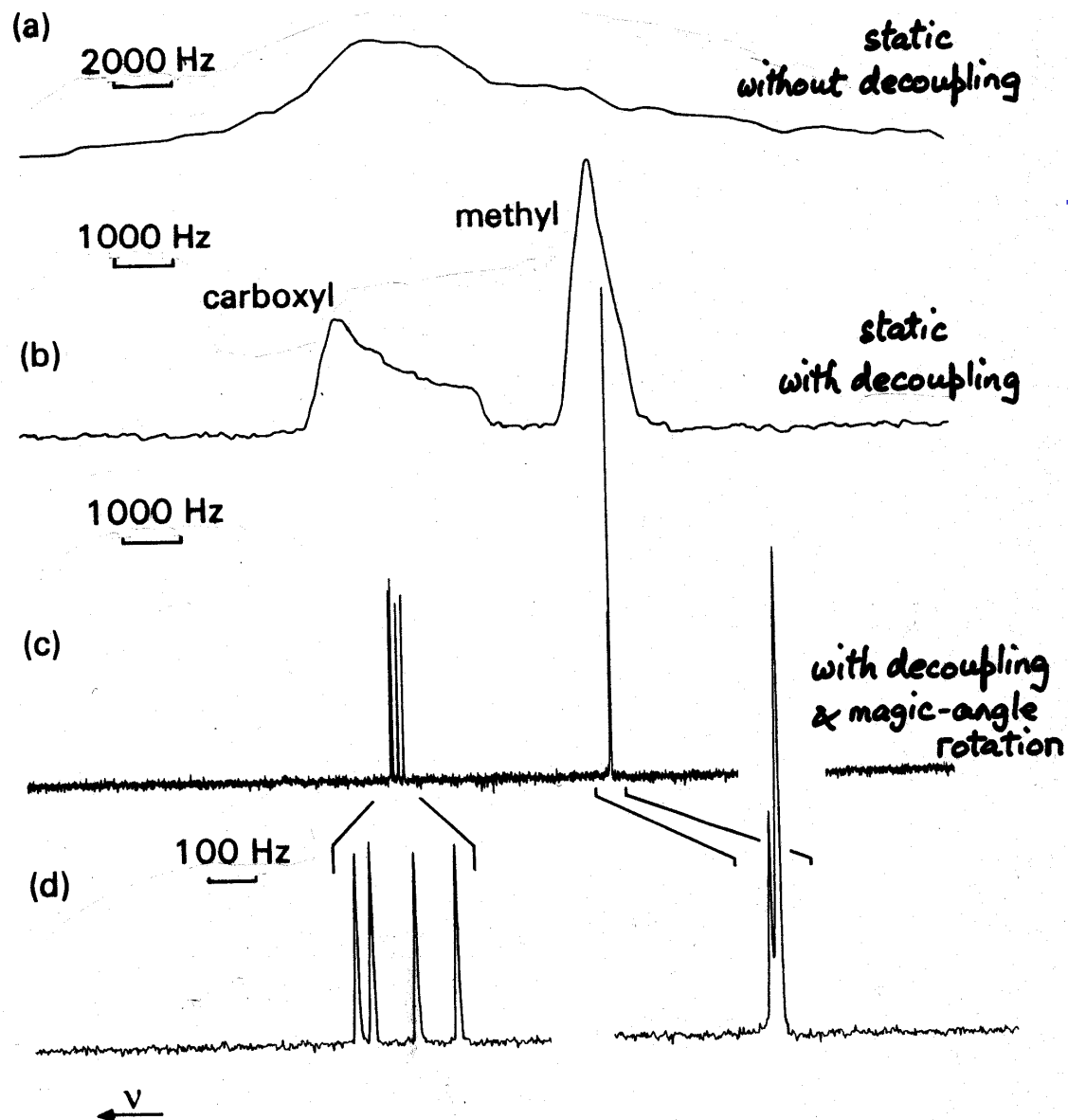
But T_{CP} VARIES for DIFFERENT C–H RELATIONS

— inefficient for quaternary carbons

CARBON-13 SPECTRA of
MICROCRYSTALLINE
CALCIUM ACETATE
HEMIHYDRATE



22.6 MHz



PROTON SPECTRA of HYDROGEN BONDS

- **COMBINED ROTATION & MULTIPLE-PULSE SPECTROSCOPY (CRAMPS)**
WAHUHA MREV8
- **FREQUENCY-SWITCHED LEE-GOLDBURG OPERATION (FSLG) with MAS**
- **VERY FAST MAS**
- **TWO-DIMENSIONAL SPECTRA (HETCOR)**

SHIELDING TENSORS

&

SPINNING SIDEBAND ANALYSIS

SHIELDING TENSOR PARAMETERS: DEFINITIONS

ISOTROPIC SHIELDING

$$\sigma_{\text{iso}} = \frac{1}{3} (\sigma_{\text{XX}} + \sigma_{\text{YY}} + \sigma_{\text{ZZ}})$$

SHIELDING ANISOTROPY

$$\zeta = \sigma_{\text{ZZ}} - \sigma_{\text{iso}}$$

SHIELDING ASYMMETRY

$$\eta = (\sigma_{\text{YY}} - \sigma_{\text{XX}}) / \zeta$$

Components labelled: $|\sigma_{\text{ZZ}} - \sigma_{\text{iso}}| \geq |\sigma_{\text{XX}} - \sigma_{\text{iso}}| \geq |\sigma_{\text{YY}} - \sigma_{\text{iso}}|$

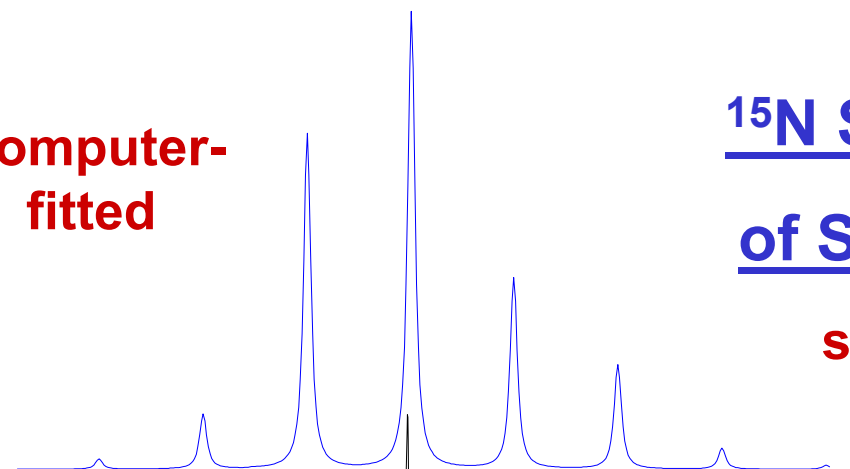
η ranges from 0 to 1

For axially symmetric cases, $\zeta = \sigma_{\parallel} - \sigma_{\perp}$, so $\eta = 0$

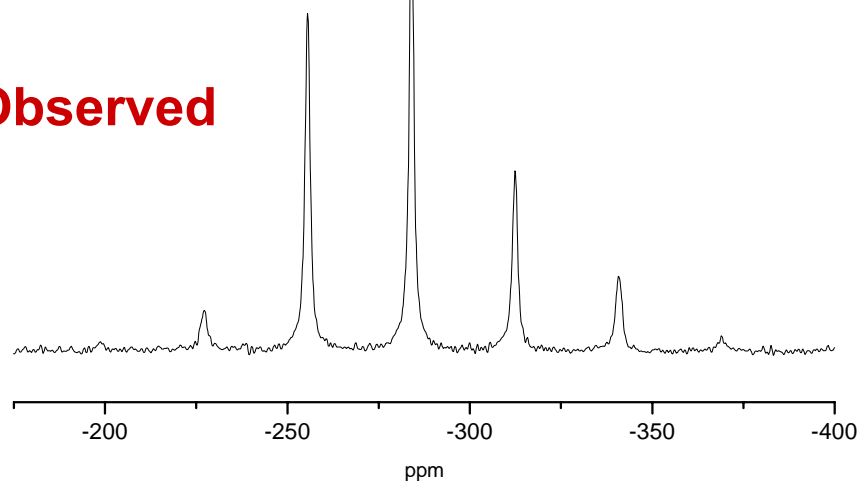
ζ can be positive or negative

Alternative definition for anisotropy: $\Delta\sigma = \sigma_{\text{ZZ}} - \frac{1}{2}(\sigma_{\text{XX}} + \sigma_{\text{YY}})$

Computer-fitted



Observed

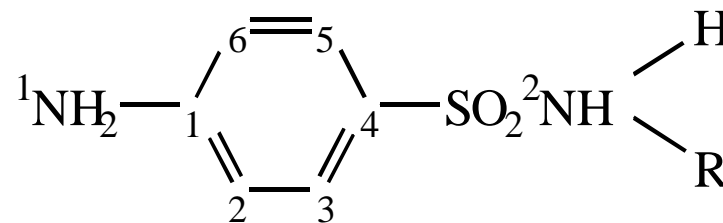


^{15}N SPECTRUM of the β FORM
of SULFANILAMIDE – for N(2)

showing spinning sidebands

[Spin rate 587 Hz]

$\zeta = 71.2$ ppm; $\eta = 0.4$



R = H

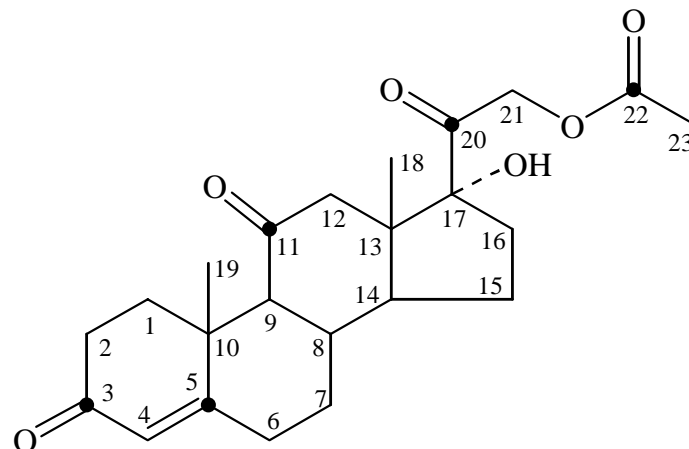
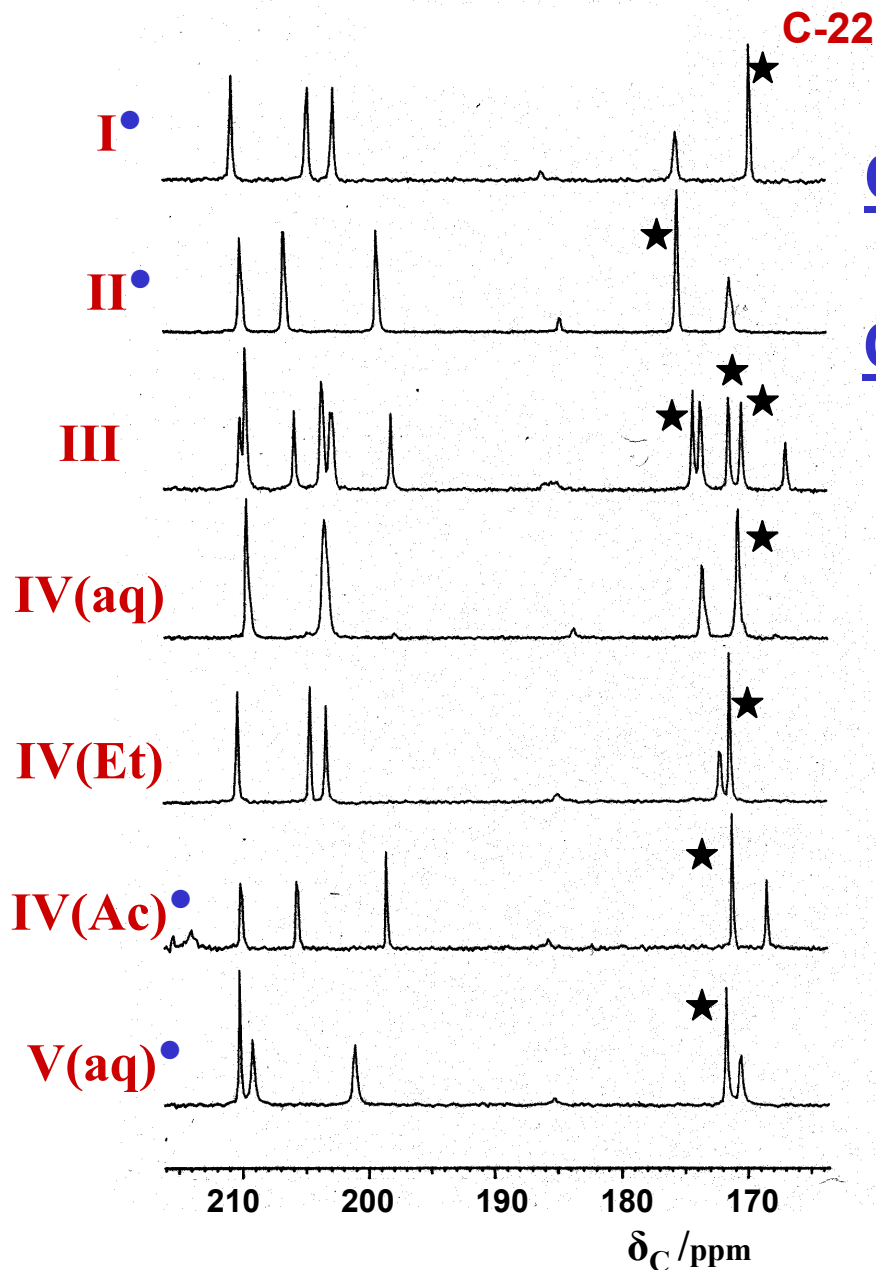
DISTINGUISHING POLYMORPHS & SOLVATES

and

LOCATING HYDROGEN BONDS

CARBON-13 CPMAS SPECTRA of CORTISONE ACETATE FORMS


(high-frequency region only)



- crystal structure known

See E.A. Christopher, R.K. Harris & R.A. Fletton,
Solid state NMR 1 (1992) 93

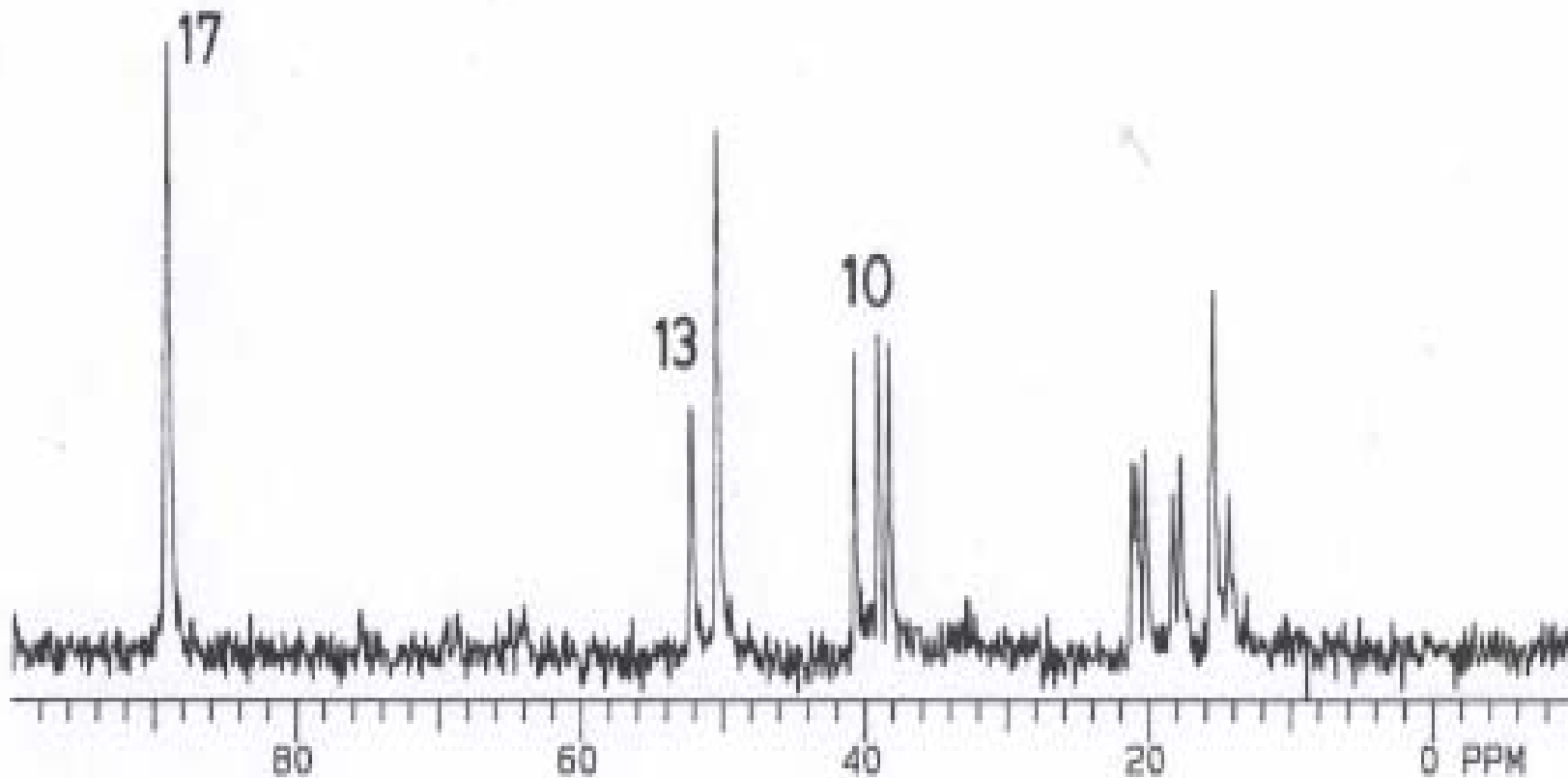
CORTISONE ACETATE SPECTRA

- DIFFERENT FORMS GIVE DIFFERENT SPECTRA
- NUMBER OF PEAKS  CRYSTALLOGRAPHIC ASYMMETRIC UNIT:
3 MOLECULES for FORM III; ONE MOLECULE OTHERWISE
- PEAK ASSIGNMENTS MADE from SHIELDING ANISOTROPY & ASYMMETRY*
- C-5 & C-22 PEAKS CROSS OVER; ISOTROPIC SHIFT OF C-3 ALSO VARIES
- INTERPRETATION RELATES SHIFT TO HIGH FREQUENCY WITH HYDROGEN BONDING
- AGREEMENT WITH XRD for 4 of the 7 FORMS
- SO H-BONDING in the other 3 FORMS DETERMINED BY NMR
- FOR FORM 3, TWO of the INDEPENDENT MOLECULES H-BOND *via* C-3 & ONE *via* C-22
- SIGNALS from SOLVATING MOLECULES (e.g. ACETONE) ARE DETECTED
- * ζ & η are characteristically different for ethylenic, carbonyl & carboxyl groups

C-13 SPECTRUM OF CORTISONE ACETATE FORM III

SHOWING CRYSTALLOGRAPHIC SPLITTINGS

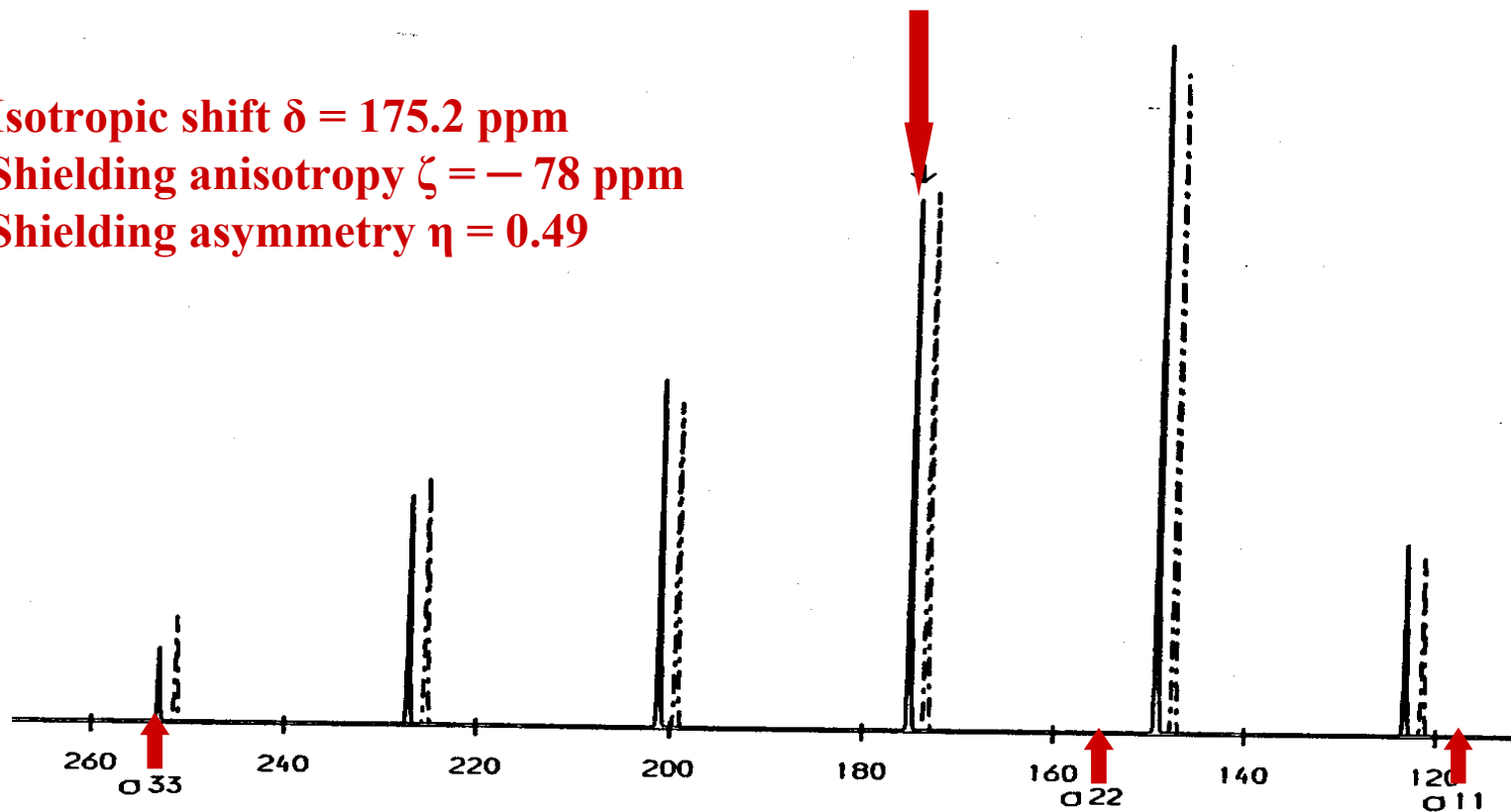
1421



DIPOLAR DEPHASING

SPINNING SIDEBAND ANALYSIS
CARBON-13 CPMAS SPECTRUM
CORTISONE ACETATE FORM II: C-22 CARBON

Isotropic shift $\delta = 175.2$ ppm
Shielding anisotropy $\zeta = -78$ ppm
Shielding asymmetry $\eta = 0.49$



Solid line (with shift scale): experimental
Dashed line (offset): computer-fitted

Spinning rate 1308 Hz

SHIELDING TENSOR PARAMETERS

 $\zeta(\text{ppm})/\eta$

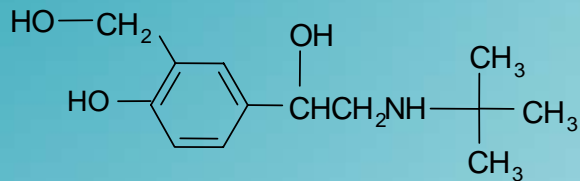
CORTISONE ACETATE	C-5 (C=C)	C-22 (ester CO)	C-3 (carbonyl)
	ζ η	ζ η	ζ η
I	103 / 0.76●	-77 / 0.04	108 / 0.05
II	117 / 0.69	-76 / 0.41●	105 / 0.21
IVac	89 / 0.67	-72 / 0.09●	93 / 0.04
IVet	108 / 0.70●	-74 / 0.00	110 / 0.15
Vaq	101 / 0.79	-78 / 0.13●	109 / 0.08
IVaq	111 / 0.65●	-78 / 0.00	[109 / 0.14]
	HIGH η	NEGATIVE ζ	
TESTOSTERONE α form	{ 117 / 0.65 111 / 0.66	- -	109 / 0.00 103 / 0.00

The data for cortisone acetate assume crossover of C-22 and C-5 signals according to centreband peak heights.

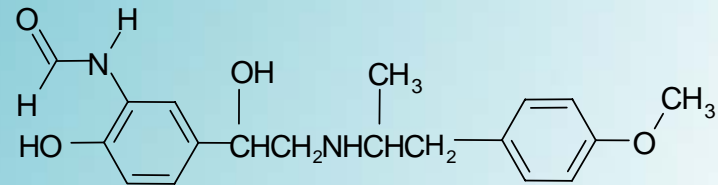
- Indicates the higher frequency (C-5 or C-22)

QUANTIFICATION

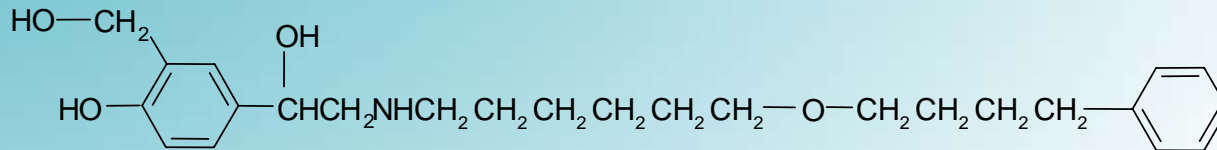
Chemical structures of β_2 -agonists



Salbutamol: short side chain



Formoterol: medium side chain



Salmeterol: long side chain

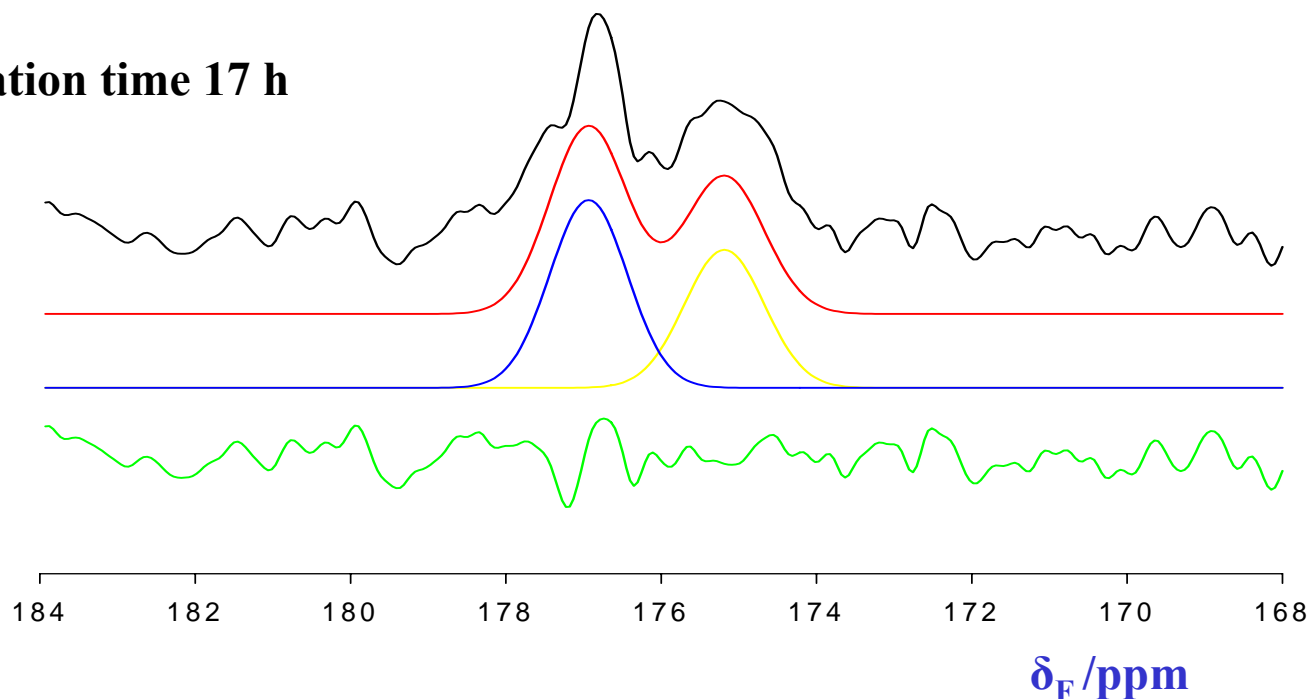


CARBO-13 CPMAS SPECTRUM of FORMOTEROL FUMARATE

2% FFA/FFD in LACTOSE

DIPOLAR DEPHASED (40 μ s) to REMOVE MOST LACTOSE INTENSITY

Accumulation time 17 h



DECONVOLUTION RESULTS: 57% dihydrate (linewidth 89 Hz)

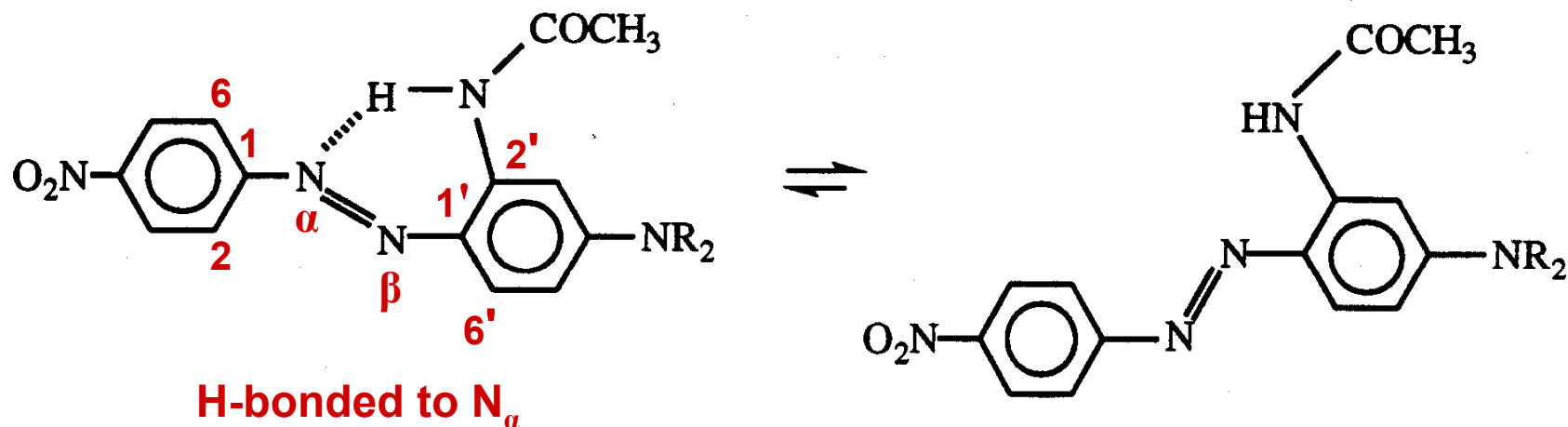
43% anhydrate (linewidth 91 Hz)

DISORDER in POLYMORPHS

&

INTRAMOLECULAR MOBILITY

CONFORMATIONS of DR278



In solution: rapid rotation of the phenylene group about the C_1-N_{α} bond.

G. McGeorge et al. J. Chem. Soc. Perkin 2, (1996) 1733;
J. Phys. Chem. A 102 (1998) 3505.

CARBON-13 SPECTRA

of DR278

2460

Black arrows indicate shifts for the 2 conformations

Polymorph A

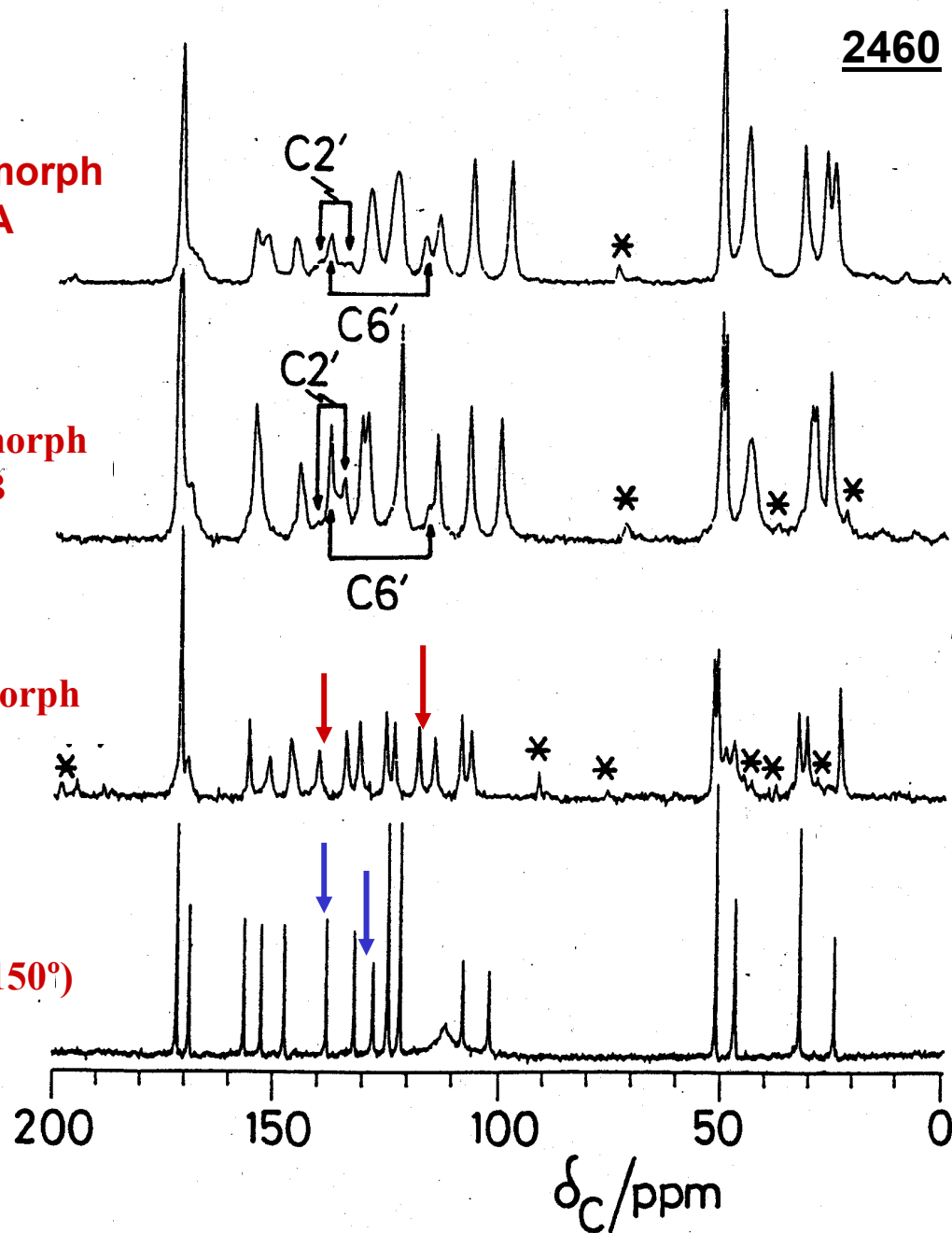
Polymorph B

Red arrows indicate shifts for single conformation

Polymorph C

Blue arrows indicate average shifts for the 2 conformations

Melt (150°)



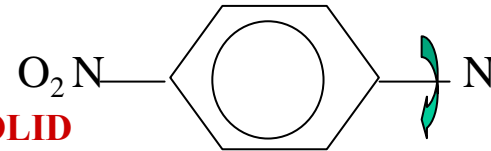
CARBON-13 SPECTRA of DR278

2892A

SPECIAL FEATURES

- The spectra of the 3 polymorphs are all different
- The melt shows 10 aromatic lines, but polymorph C shows 12

**ROTATION ABOUT
IS RAPID IN SOLUTION BUT SLOW IN THE SOLID**



- The aliphatic lines for polymorph C show doublet splittings

THE 2 CH₂CH₂CO₂CH₃ CHAINS ATTACHED TO N ARE NON-EQUIVALENT IN THE SOLID

- The lines assigned to C2' & C6' are split into 2 for polymorphs A & B

**TWO CONFORMATIONS ARE PRESENT SIMULTANEOUSLY IN THESE POLYMORPHS
— IN UNEQUAL PROPORTIONS**

- The average chemical shifts of the C2' pair of lines and of the C6' pair of lines correspond to the C2' & C6' shifts for the melt

**THE CONFORMATIONS ARE PRESENT IN APPROXIMATELY EQUAL PROPORTIONS IN THE MELT
— AND ARE RAPIDLY INTERCONVERTING**

- **QUESTION:**

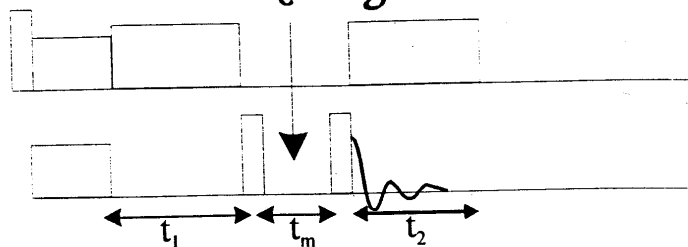
IS THE CONFORMATIONAL DISORDER IN POLYMORPHS A & B STATIC OR DYNAMIC IN NATURE?

2D EXCHANGE SPECTROSCOPY

2475

Magnetisation transfer sequence.

monitor exchange here



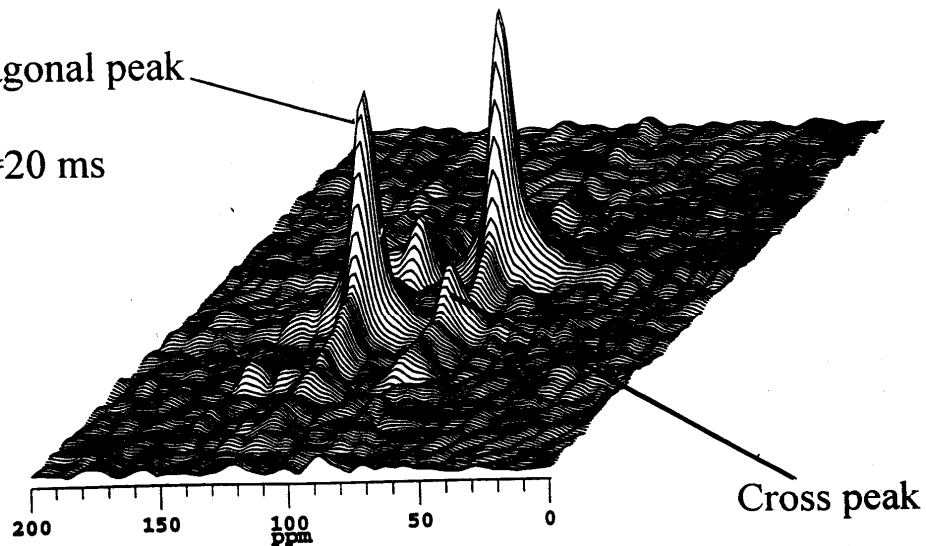
2. Exchange during mixing time creates cross peaks.

Vary t_1 time : Fix t_m . Takes long time.

$$\frac{I_{\text{diag}}}{I_{\text{cross}}} = \frac{1 + \exp(-2kt_m)}{1 - \exp(-2kt_m)}$$

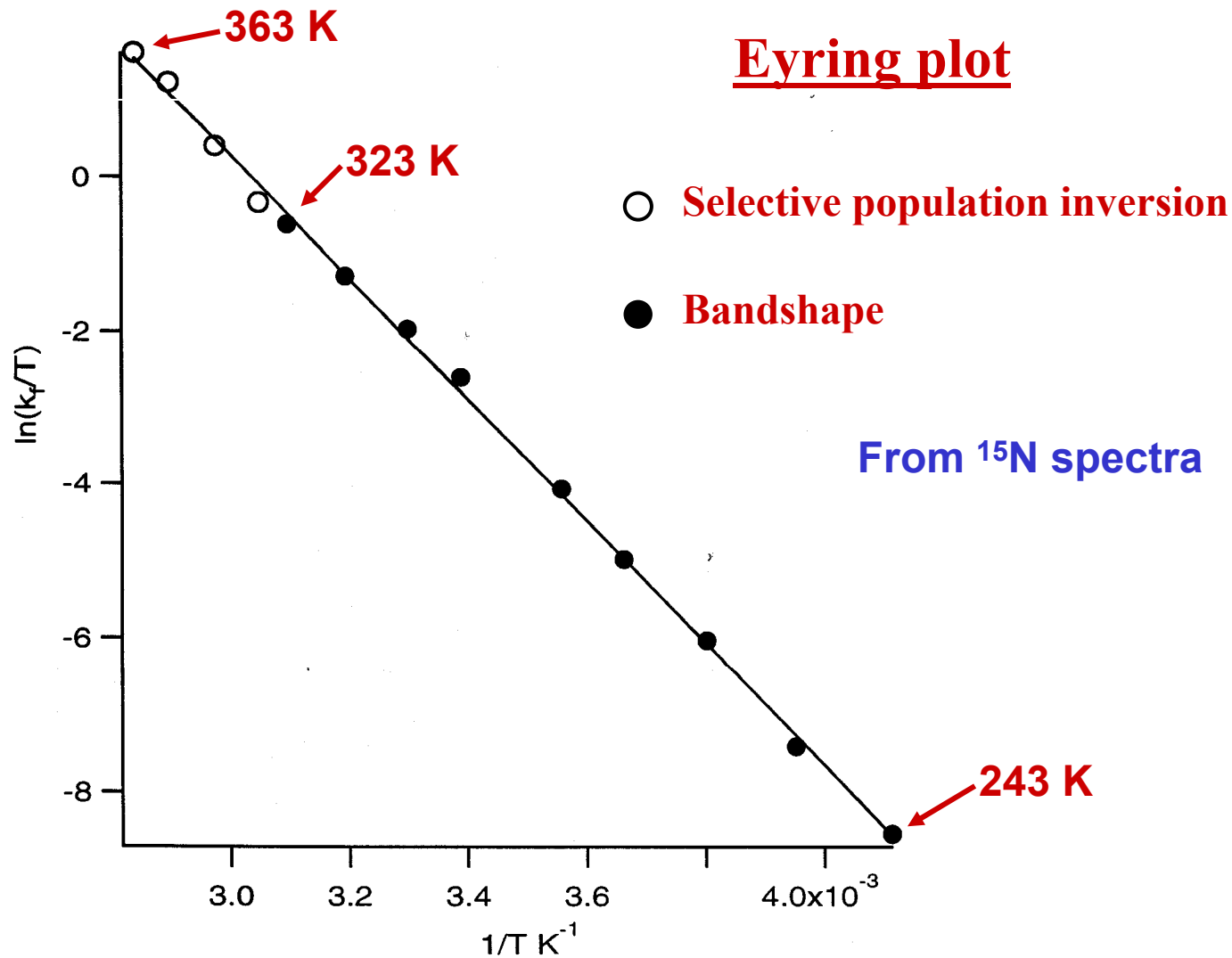
Diagonal peak

$t_m = 20$ ms



^{15}N 2D stacked plot.

EXCHANGE KINETICS for DR278 (FORM A)



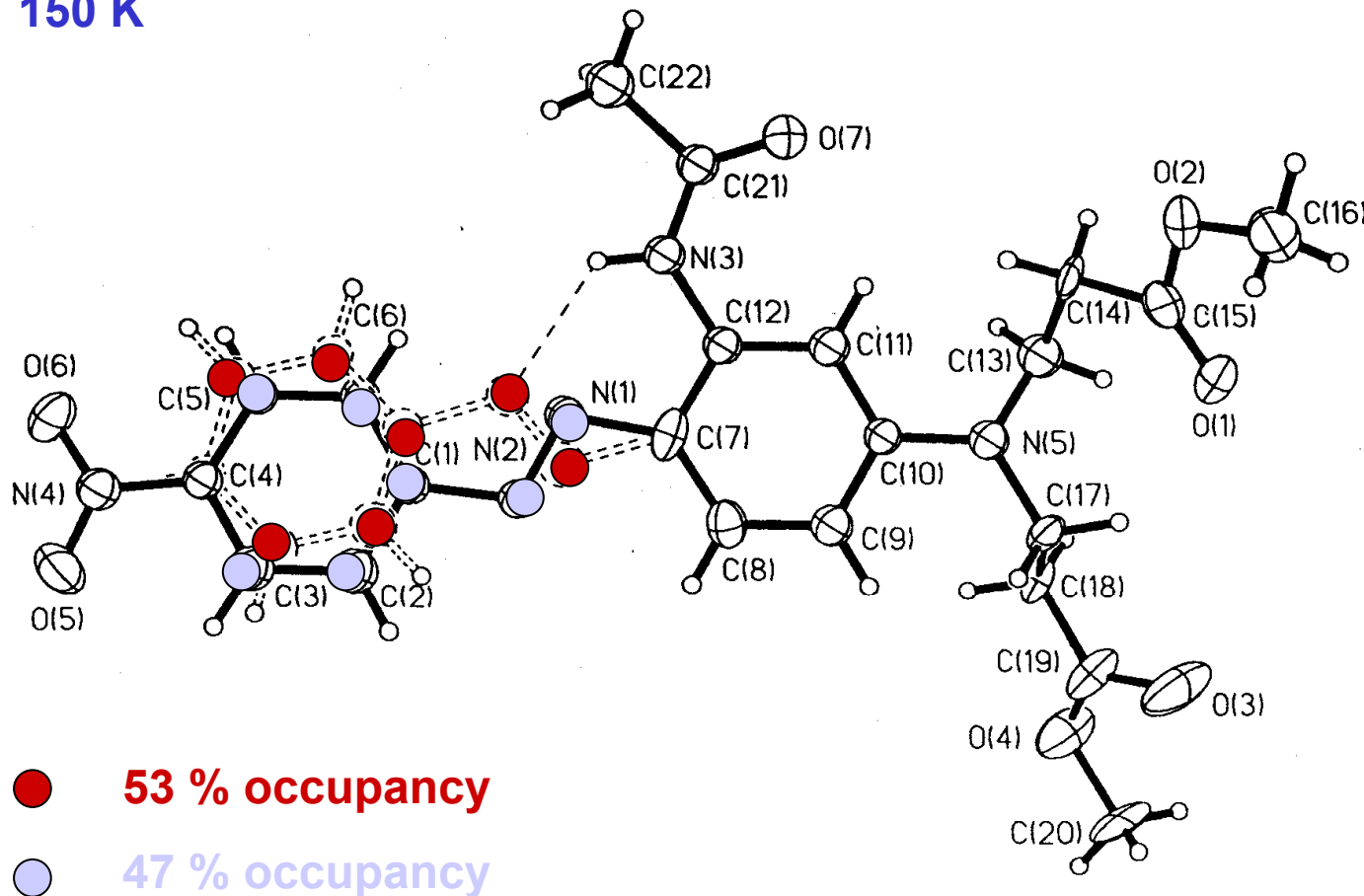
$$\Delta H^* = 63 \text{ kJ mol}^{-1}; \quad \Delta S^* = -6 \text{ J mol}^{-1} \text{ K}^{-1}; \quad \Delta G^*(298) = 65 \text{ kJ mol}^{-1}$$

STRUCTURE of CRYSTALLINE DR278, POLYMORPH A

showing disorder in the azo link (and associated phenylene ring)

150 K

2371



RELAXATION

- ***SPIN-LATTICE (LONGITUDINAL)*** T_1
motions at ca. resonance frequency (hundreds of MHz)
- ***SPIN-LATTICE in the ROTATING FRAME*** $T_{1\rho}$
motions at ca. strength of the RF (tens of kHz)
- ***SPIN-SPIN (TRANSVERSE)*** T_2
motions at ca. zero frequency

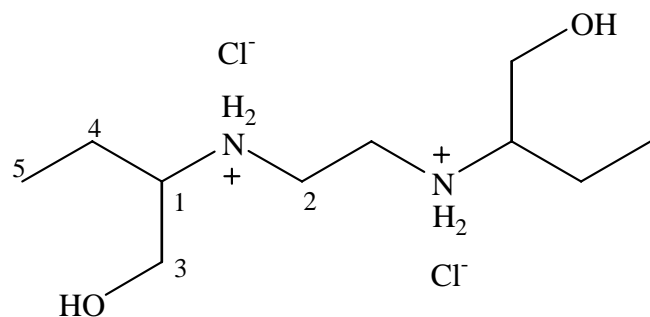
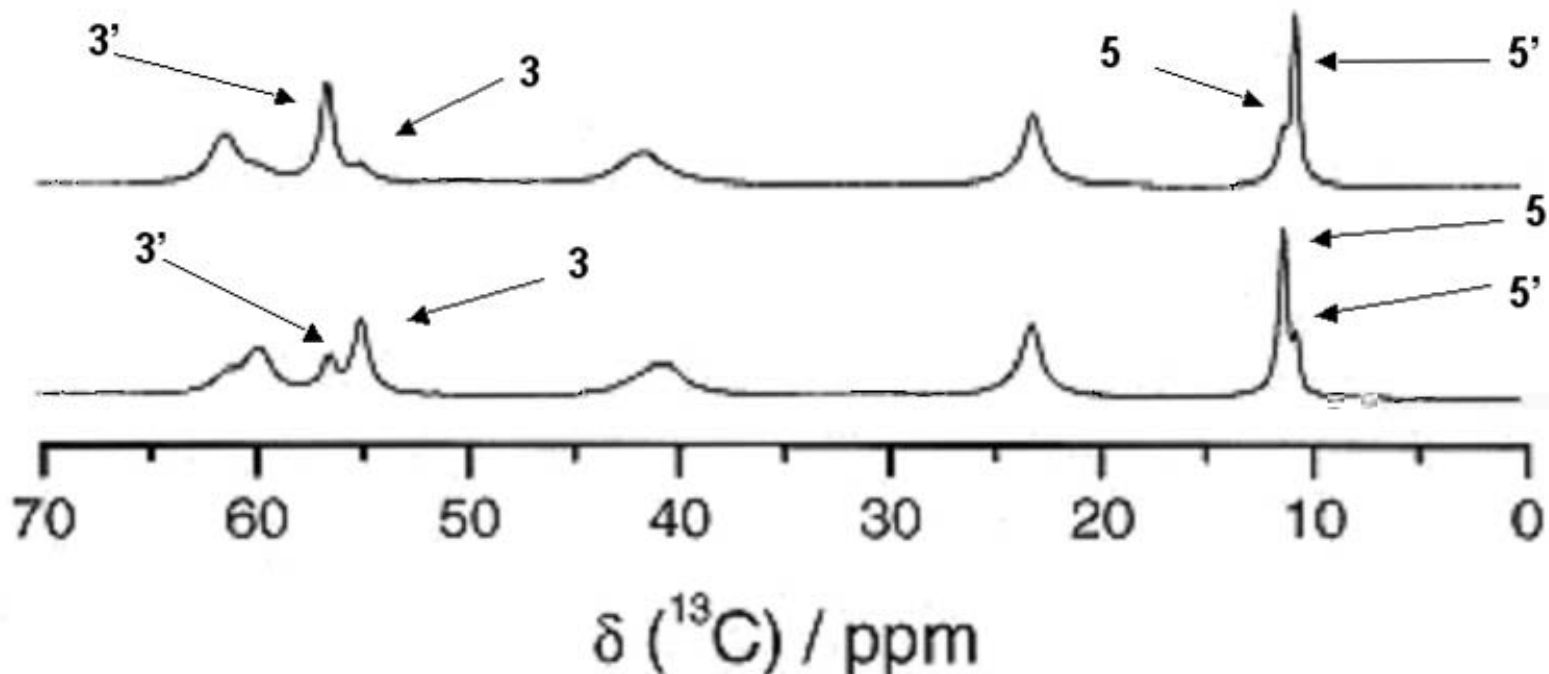
NOTE the ESSENTIAL USE OF VARIABLE TEMPERATURE

TRANSITIONS
between POLYMORPHS

CARBON-13 CPMAS SPECTRA of ETHAMBUTOL HYDROCHLORIDE

in a temperature gradient at two average temperatures
near the transition temperature

3223

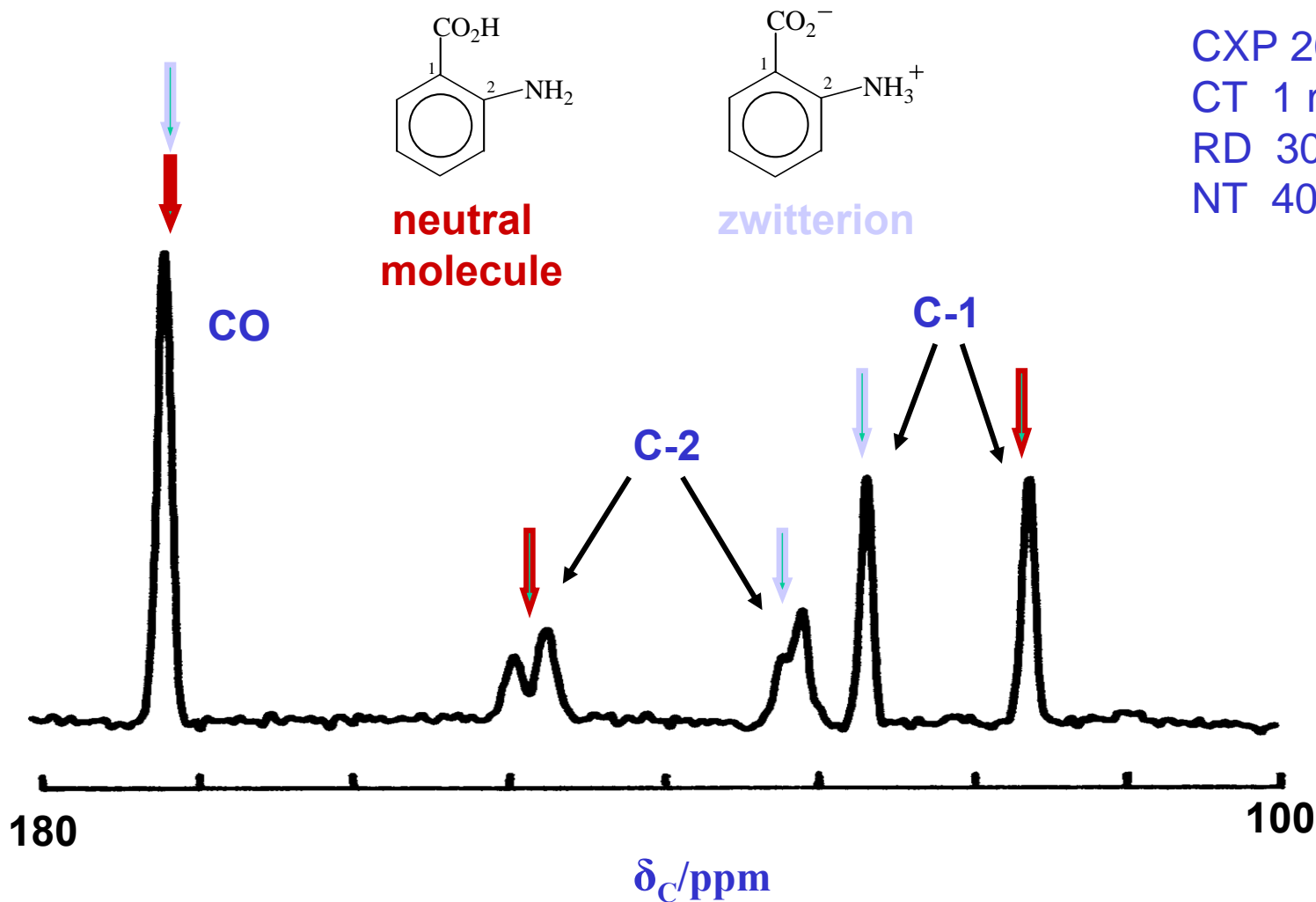


Primed numbers refer to Form I,
unprimed to Form II

J.M. Rubin-Preminger et al.,
Crystal Design & Growth **4** (2004) 431

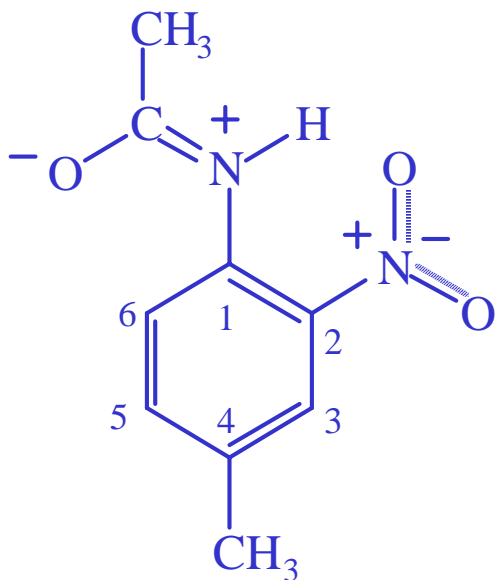
**DETECTING
TAUTOMERIC FORM
in POLYMORPHS**

DIPOLAR DEPHASING



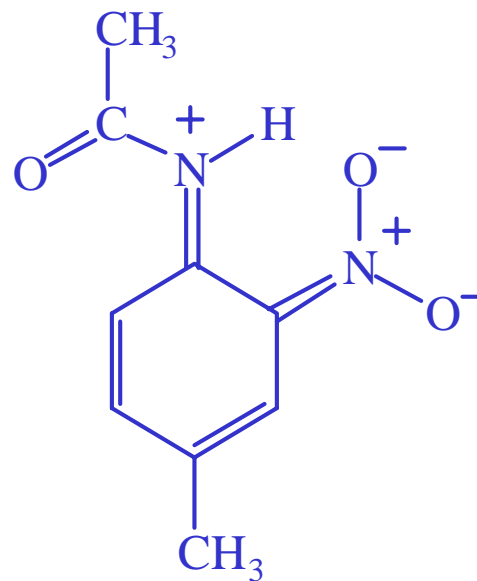
LOCATING HYDROGEN ATOMS in HYDROGEN BONDS

STRUCTURES of MNA



White form

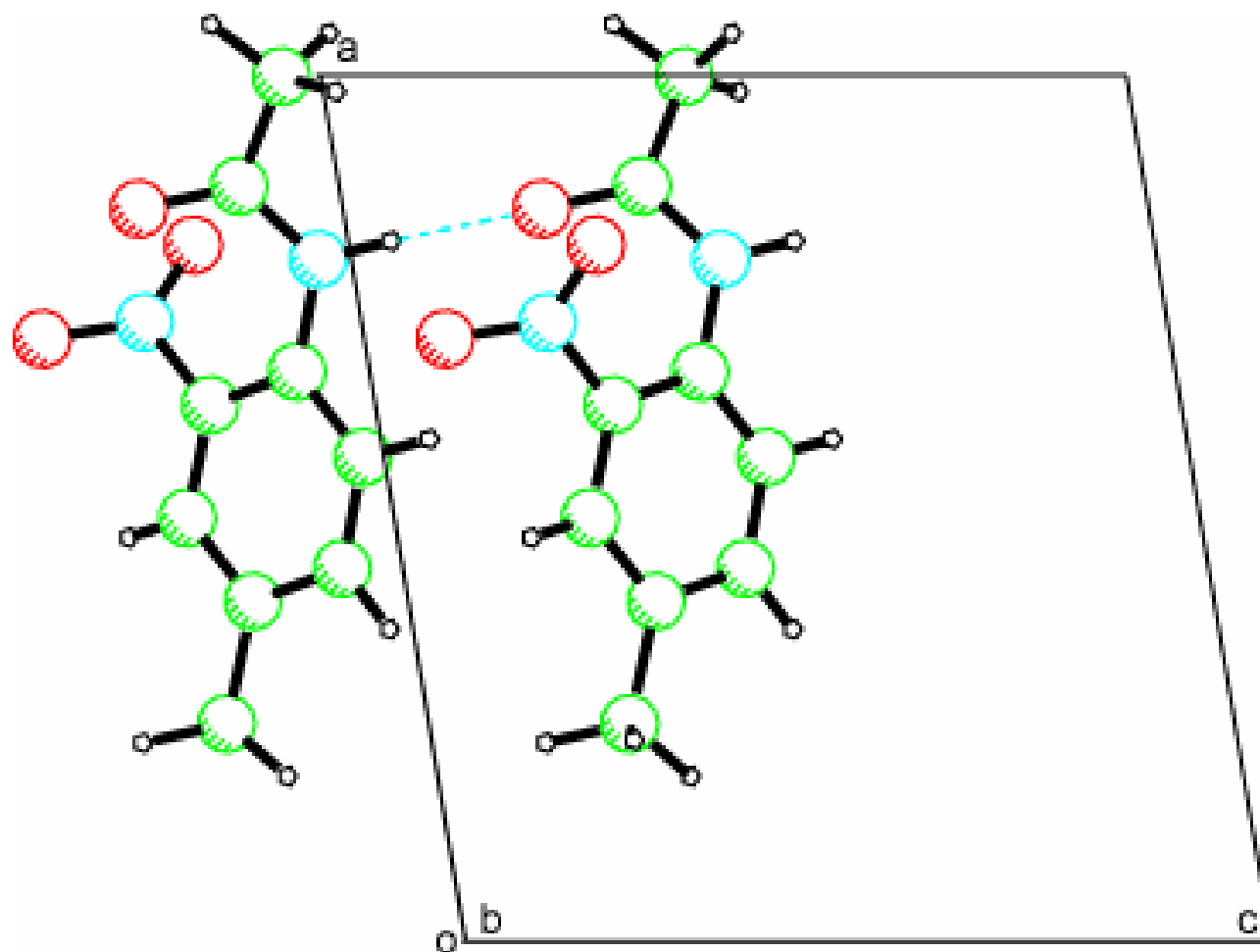
from DMSO solution



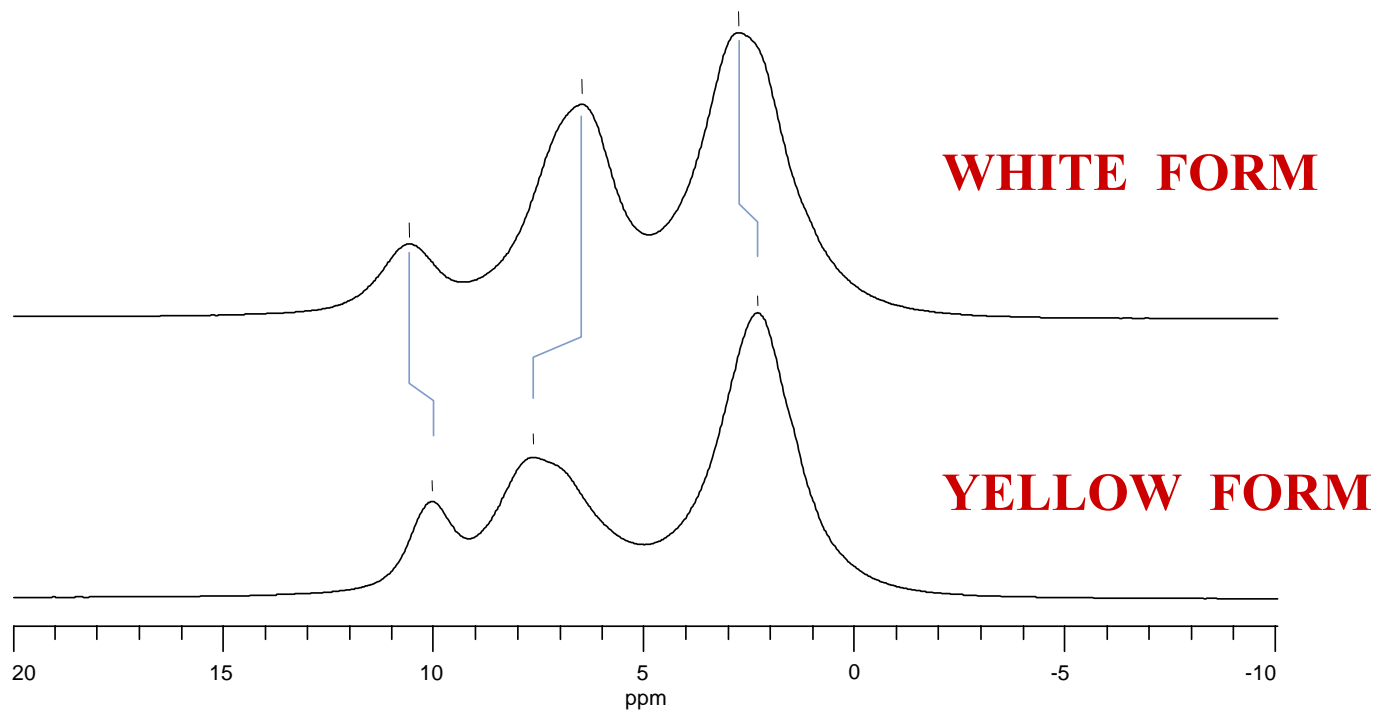
Yellow form

from CHCl₃ solution

H-BONDED DIMER OF MNA (WHITE FORM)

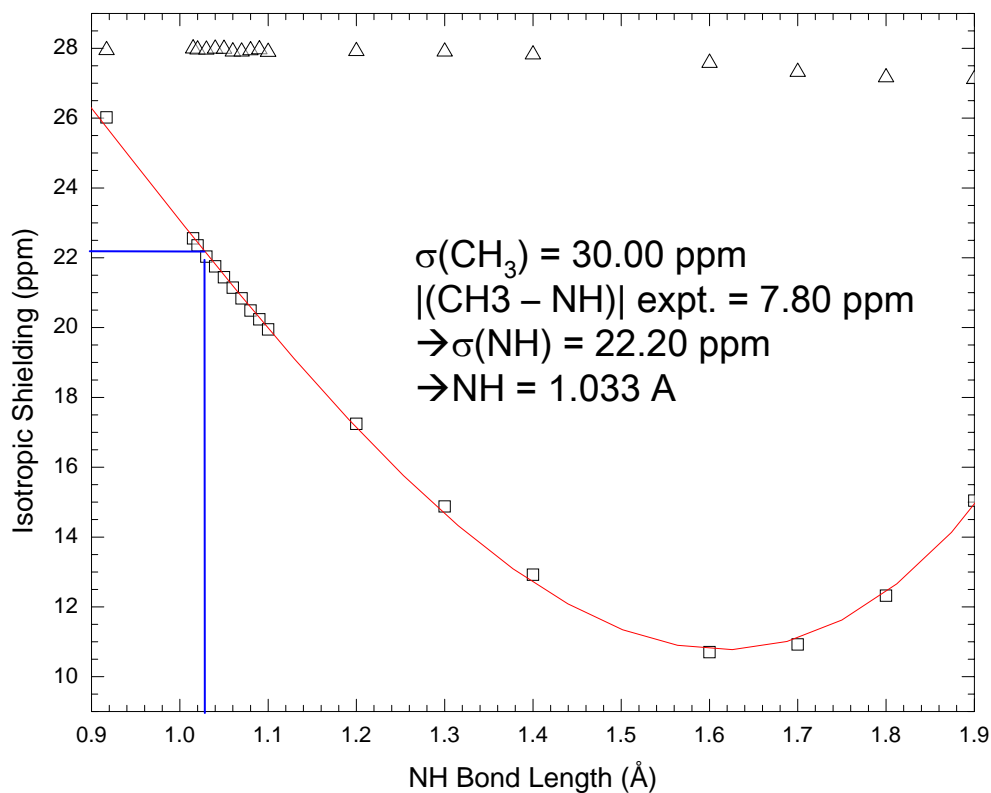


FAST MAS PROTON SPECTRUM OF MNA



Effect of NH Bond Length on ^1H NMR Shielding

3117A



- ④ ^1H shielding is strongly dependent on NH bond length.
- ④ Refined NH bond length is 1.033 Å

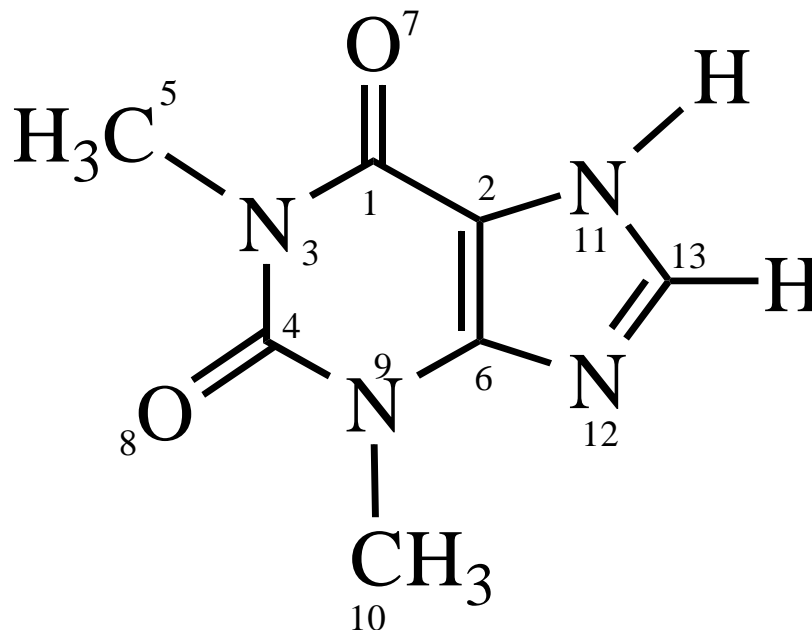
H-BOND RESULTS FOR MNA

(WHITE FORM)

N.....O	from diffraction results	2.860 Å
N–H	from diffraction results	0.917 Å
N–H	from NMR/computation	1.033 Å

POLYMORPHIC FORM IDENTIFIED
by a COMBINATION of POWDER
XRD, NMR
& MOLECULAR MODELLING

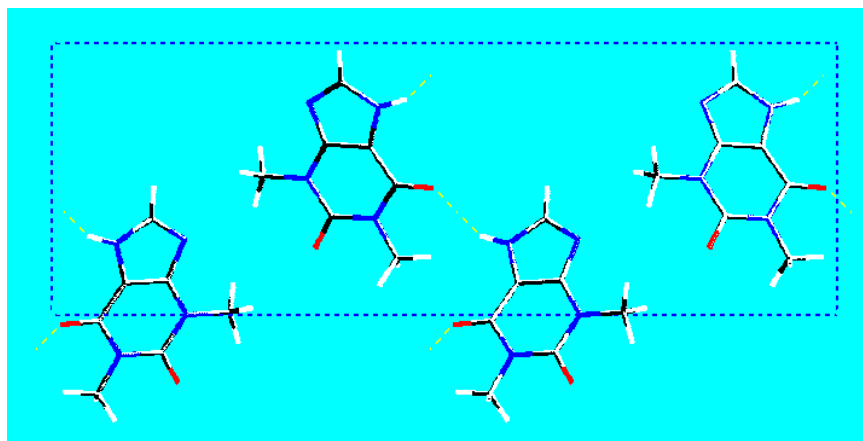
THEOPHYLLINE



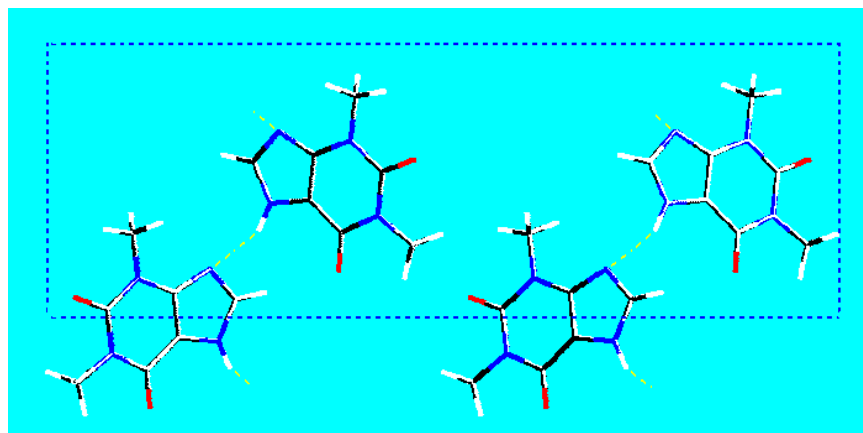
- **TWO STRUCTURAL MOTIFS FIT THE POWDER XRD DATA and the ENERGY MINIMISATION PROCEDURE (within the same unit cell)**
- **DO THESE EXIST AS POLYMORPHS?**
- **WHICH ONE IS THE COMMERCIAL PRODUCT?**

THEOPHYLLINE: ALTERNATIVE STRUCTURES

**II: N–H....O
HYDROGEN
BOND**



**I: N–H....N
HYDROGEN
BOND**



THEOPHYLLINE: ^{15}N CHEMICAL SHIFTS ($\delta_{\text{N}}/\text{ppm}$)

	EXPT	CALC	EXPT-CALC	CALC	EXPT-CALC	CALC	EXPT-CALC
N3	-222	-221	-1	-222	0	-222	0
N9	-264	-261	-3	-262	-2	-254	-10
(NH)	-214	-239	+25	-218	4	-226	+12
N12	-158	-139	-19	-157	-1	-120	-38
	MAS	MONOMER		NH...N TRIMER		NH...O TRIMER	

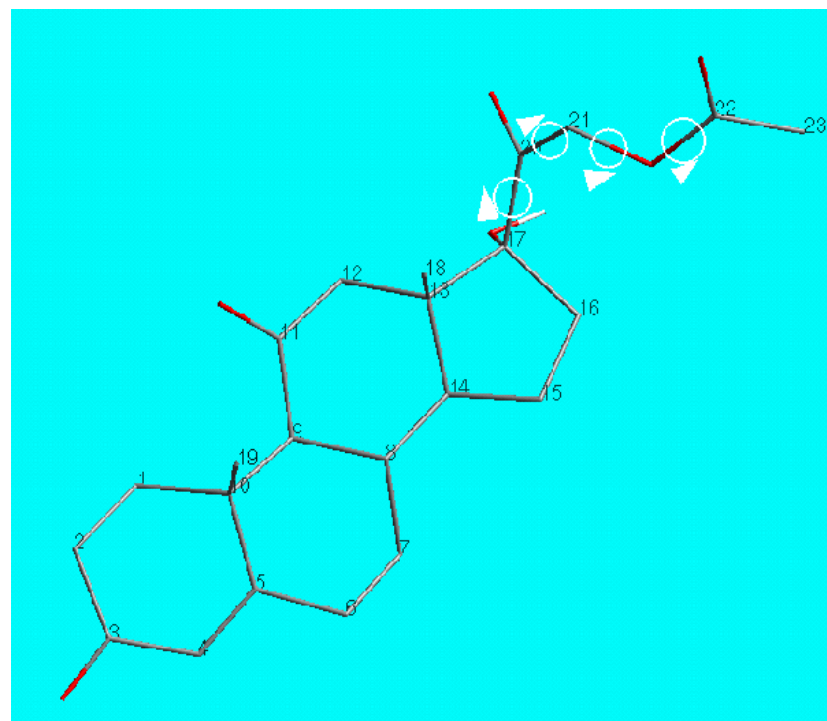
CALCULATIONS by D. Gauss 4.1 with 6-31 g* basis set
 BPW91/TZVP level of theory
 LORG method for shielding

R.K. Harris & co-workers, J. Phys. Chem. B. **105**, 5818 (2001).

**SOLVING STRUCTURES from a
COMBINATION of
MASNMR & POWDER XRD**

Information on H-bonding from SSNMR

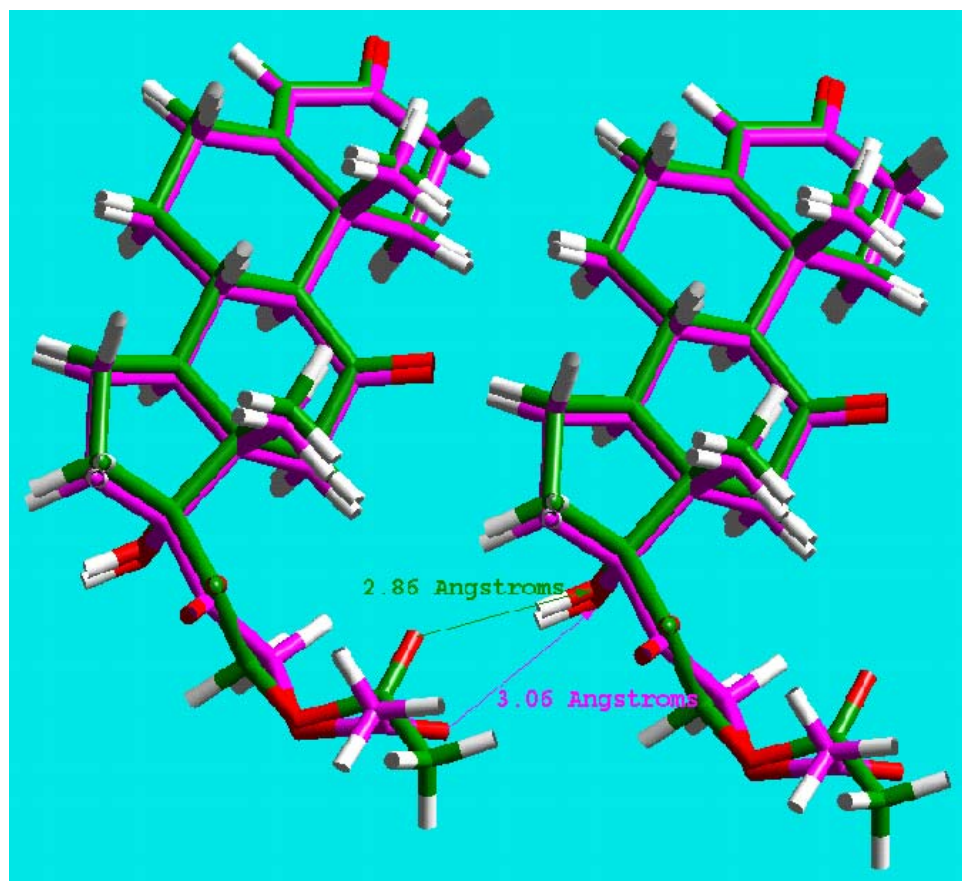
- In form I, the intermolecular hydrogen bonding is of the head-to-tail type O(17)-H—O(3).
- In form II, the intermolecular hydrogen bonding is of the head-to-head type O(17)-H—O(22).
- In form III, there are three independent molecules in the asymmetric unit, two molecules hydrogen bonded through O(17)-H—O(3) and one through O(17)-H—O(22).



CORTISONE ACETATE FORM II

COMPARISON of the SIMULATED ANNEALING RESULT

with RESTRAINT (in PURPLE) and the REPORTED STRUCTURE (in GREEN)



CORTISONE ACETATE FORM II

STRUCTURAL ANALYSIS from POWDER XRD DATA

Parameters describing the best trial structures found in simulations with and without a soft distance restraint of 2.9 Å for the O17 to O22.

Parameter	Torsion 1/°	Torsion 2/°	Torsion 3/°	Torsion 4/°	Distance O17-O22/Å	Angle O17-H17-O22/°
Without restraint	-91.5	115.0	110.9	55.0	3.84	150.9
With restraint	-71.9	-177.3	-103.7	111.0	3.06	151.8
Crystal	-94.4	168.5	-82.0	178.1	2.86	164.5

POWDER XRD + SOLID-STATE NMR: CORTISONE ACETATE

conclusions

- **Trial structure generation using simulated annealing approach from laboratory-sourced powder X-ray diffraction data successful for form II cortisone acetate.**
- **However, powder data insufficient to fully constrain side-chain conformation: several distinct arrangements agree with data equally well.**
- **Soft NMR-derived distance constraint does direct parameter most labile with respect to powder data, i.e. acetate group torsion.**
- **However, a second restraint is required from NMR to properly reproduce the structure obtained from single-crystal X-ray data.**

DETERMINATION of INTERATOMIC DISTANCES

DIPOLAR COUPLING CONSTANT

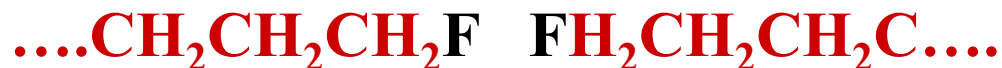
$$D_{AX} = (\mu_0/4\pi)(h/4\pi^2)\gamma_A\gamma_X/(r_{AX})^3$$

in frequency units

- *PROVIDES AVERAGE of $(r_{AX})^{-3}$*
 - *at the temperature of measurement*
 - *over any motion along r*
- *r WILL NOT BE THE SAME AS THAT FROM DIFFRACTION*
- *MOTION PERPENDICULAR TO r MAKES COMPLICATIONS*

MOBILITY EFFECTS for an INCLUSION COMPOUND

SYSTEM: α , ω -DIFLUOROALKANE in UREA



- The HOST-GUEST ARRANGEMENT is INCOMMENSURATE
- ^{19}F SPECTRUM with PROTON DECOUPLING

 classic isolated spin pair

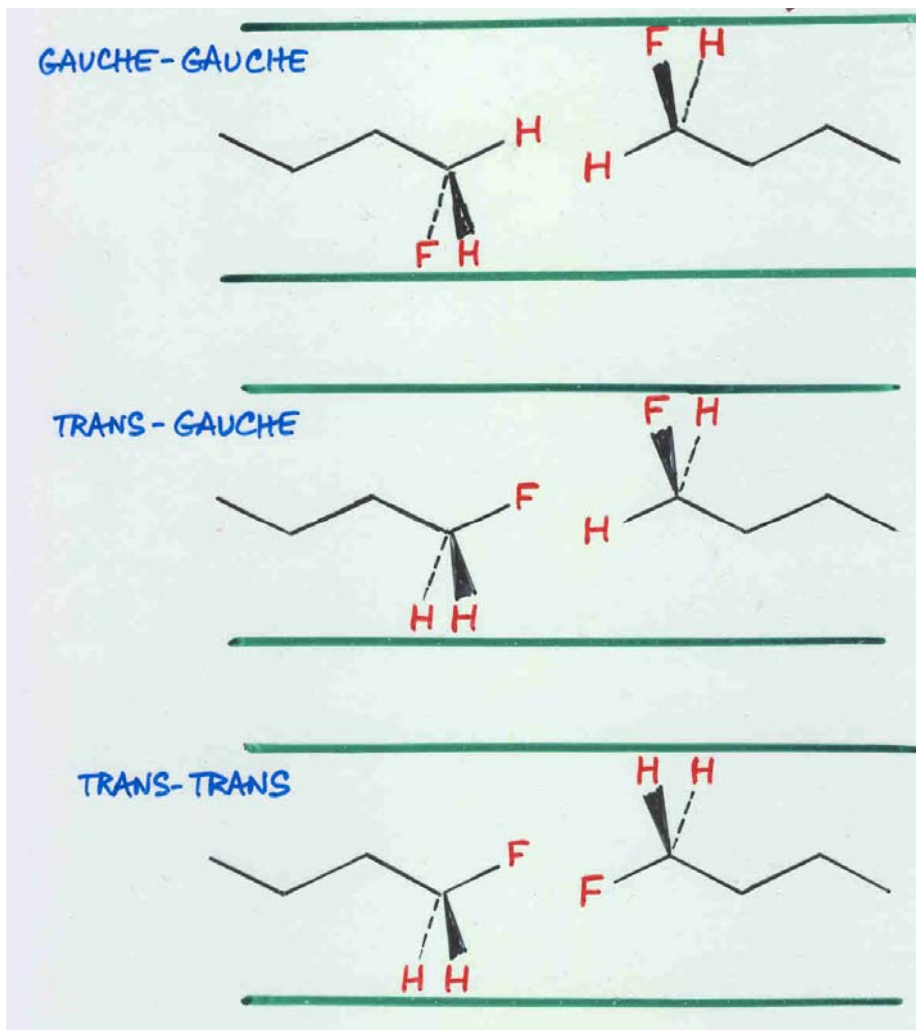
(from ^{19}F nuclei in adjacent guest molecules)

- DIPOLE COUPLING CONSTANT GIVES INTERATOMIC (INTERMOLECULAR) DISTANCE
- BUT AVERAGING CAUSED BY MOBILITY and/or DISORDER MUST BE CONSIDERED

FLUOROALKANE/UREA INCLUSION COMPOUND

END-GROUP SITUATIONS FOR ADJACENT MOLECULES

(coplanar chains with mutually staggered atoms, though this is not essential)



degeneracy 4

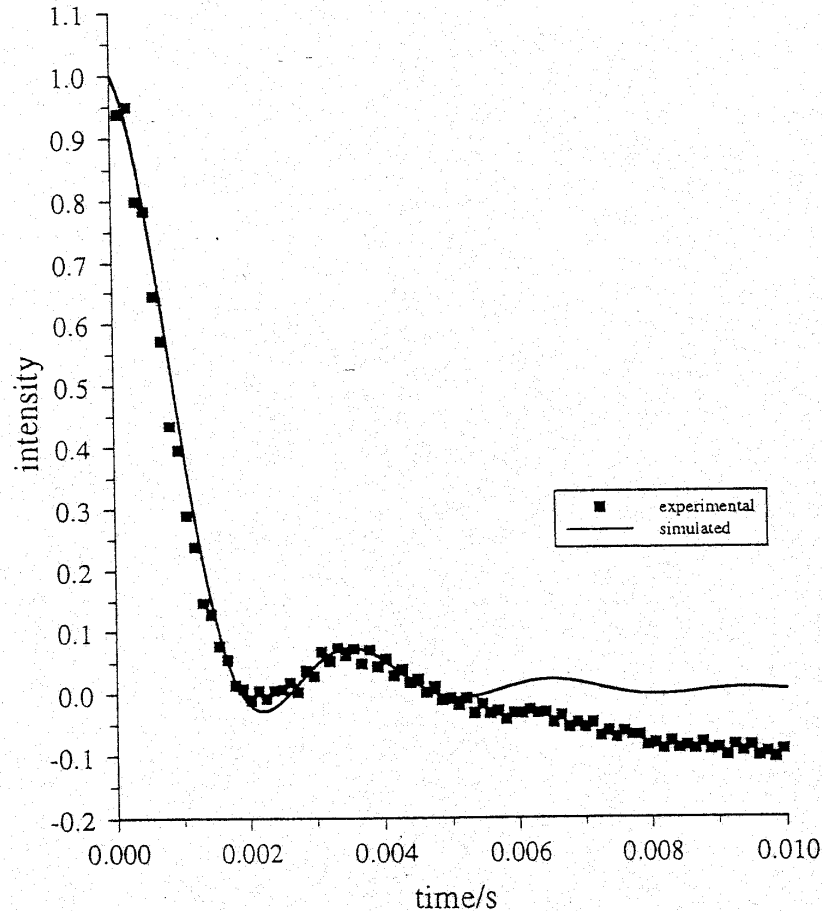
2588A

degeneracy 4

degeneracy 1

MELODRAMA RESULTS

at the $N = 4$ matching condition ($N = \gamma B_1 / 2\pi\nu_r$)



RESULT: $D^{\text{eff}}(\text{FF}) = 995 \text{ Hz}$

1,10-DIFLUORODECANE/UREA INCLUSION COMPOUND

CONCLUSIONS

- ❖ The intermolecular average F,F distance is:

$$\langle r \rangle = 4.75 \text{ \AA}$$

- ❖ This is consistent with a distribution over all gg and tg forms, with no angular preference.
- ❖ Absence of tt forms

A. Nordon, E. Hughes & R.K. Harris

CONCLUSIONS

Magic-angle spinning NMR contributes significantly to polymorph detection and characterisation:

- ❖ **COMPLEMENTARY to DIFFRACTION TECHNIQUES**
- ❖ **INFORMATION on MOLECULAR SYMMETRY**
- ❖ **INFORMATION on INTERMOLECULAR INTERACTIONS**
- ❖ **INFORMATION on MOLECULAR MOBILITY**
- ❖ **INFORMATION on DISORDER**
- ❖ **INFORMATION on INTERATOMIC DISTANCES**

NMR CRYSTALLOGRAPHY

DURHAM CATHEDRAL & THE RIVER WEAR



DURHAM SOLID-STATE NMR GROUP, APRIL 2003



NMR OF SOLIDS: BOOKS

- **Chapter 6 of “Nuclear Magnetic Resonance Spectroscopy”, R. K. Harris, Longmans, latest reprint 1997.**
- **“Solid State NMR for Chemists”, C. A. Fyfe, C.F.C. Press, 1983.**
- **“Multinuclear Magnetic Resonance in Liquids and Solids – Chemical Applications”, eds. P. Granger & R. K. Harris, NATO ASI Series C, Vol. 322, Kluwer Academic Publishers, 1988.**
- **“Solid-state NMR Spectroscopy. Principles & Applications”, ed. M. J. Duer, Blackwell Science, 2002.**



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APPLICATIONS:

- ✓ **Pharmaceuticals**
- ✓ **Polymers**
- ✓ **Minerals**
- ✓ **Catalysts**
- ✓ **Fuels**
- ✓ **Pigments**
- ✓ **Sealants**
- ✓ **Wood/cellulose**

...just about anything solid(ish)

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