晶云药物第二届晶型专题技术培训

固体核磁共振在晶型研究和固态研发中的应用

主讲人：张海禄博士，副研究员
磁共振波谱与影像实验室 &分子识别与传感实验室
中科院苏州纳米技术与纳米仿生研究所
Crystal Pharmatech
苏州晶云药物科技有限公司
Email：sales@crystalpharmatech.com
电话：0512-69561921



Crystal Pharmatech
您的药物晶型研究和固态研发专家

为什么药物需要做ssNMR

为什么药物需要做固相表征

✓ 稳定性、溶解性、可加工性、生物利用度、知识产权

ssNMR能做什么

✓ ssNMR晶体学

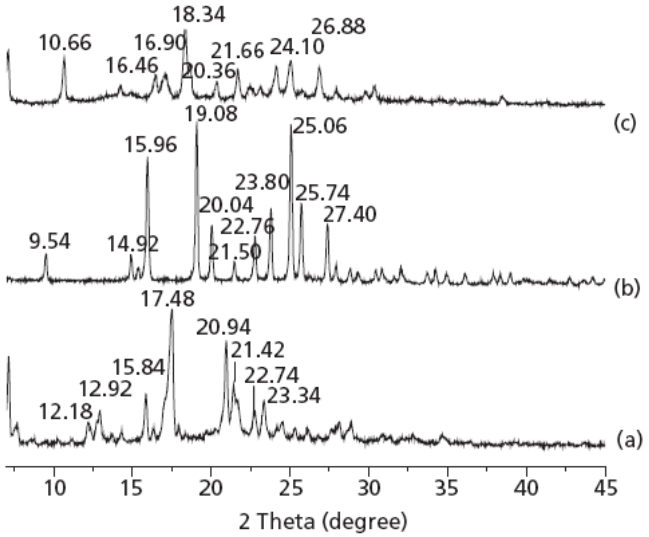
✓ **定性**：API和制剂中API的晶型（含无定型）、构象、溶剂化、水合、成盐歧化、稳定性，… *整体和表面

✓ **定量**：量化定性问题。如：多晶型混合物的定量

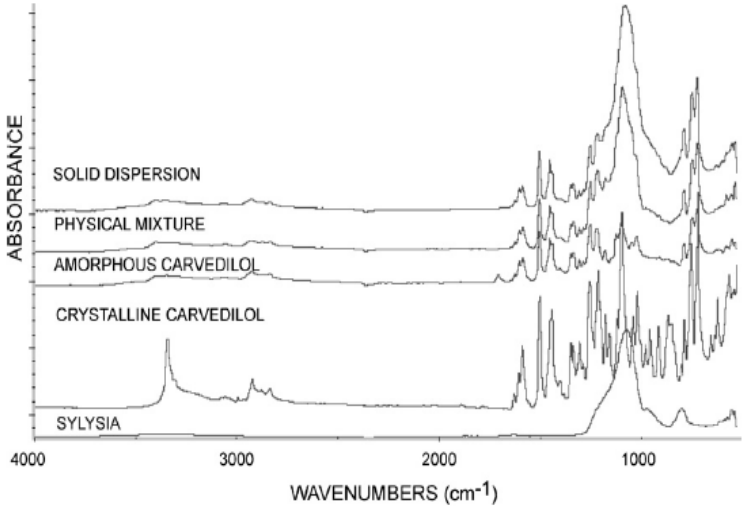
✓ **分子间相互作用**：如无定型药物的分子水平分散

ssNMR在晶型研究和固态研发中的应用

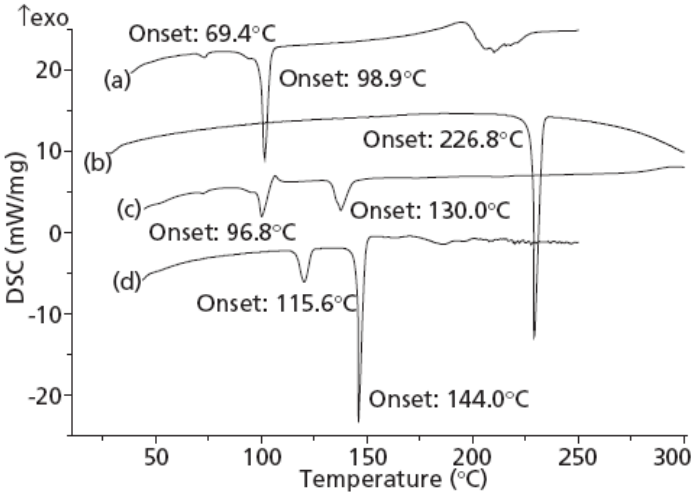
- 原料药固态存在形式定性分析指纹谱比对
- 原料药溶剂合物和残余溶剂的区别
- 多固态共存体系的定量分析
- 药物无定型分散体系分子水平分散的确认
- 药物共晶的确认



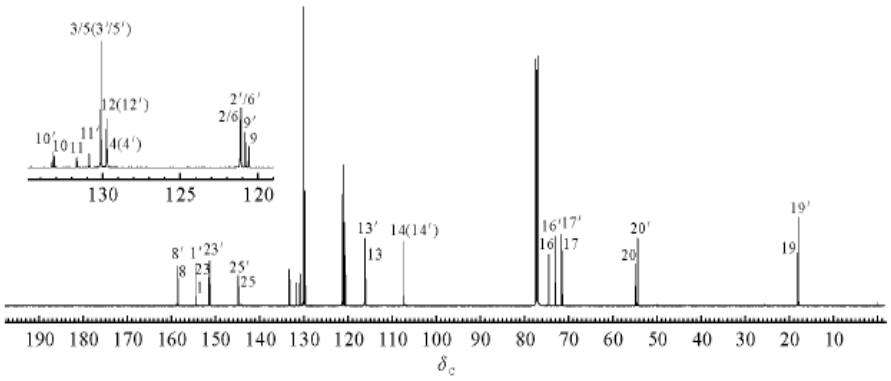
XRD: 晶面



FTIR/RAMAN：键

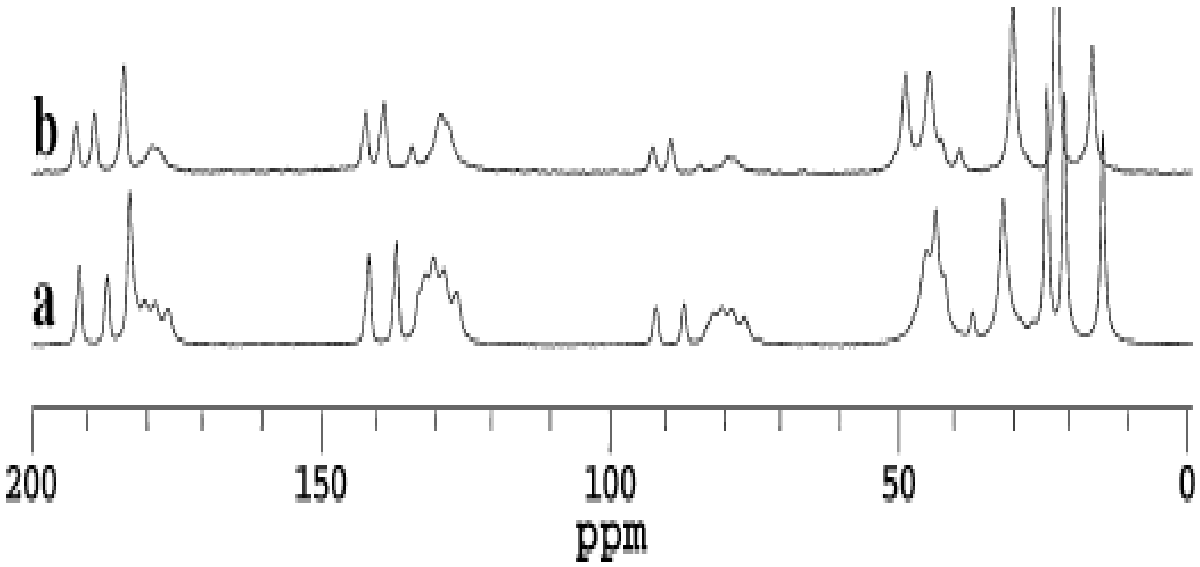


热分析：整体相变

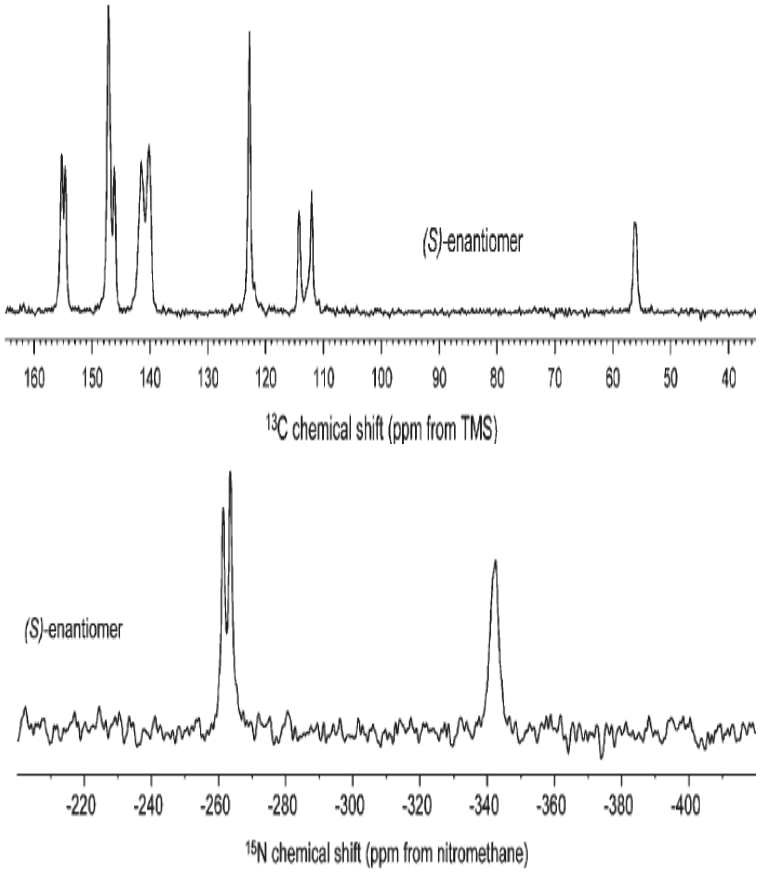


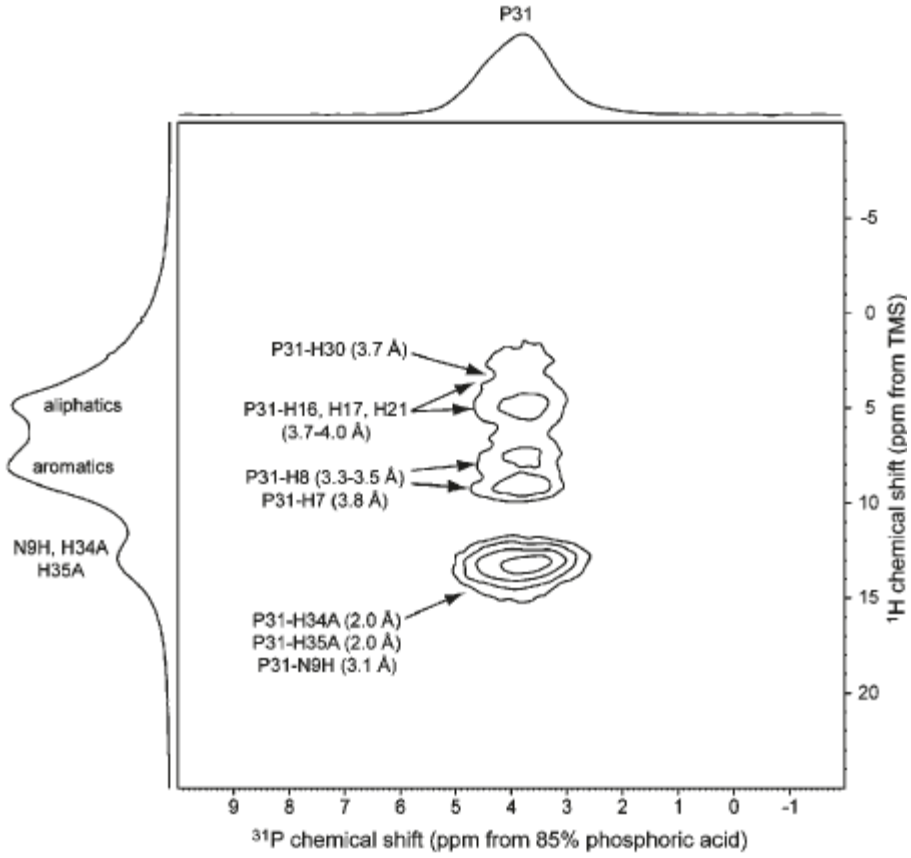
NMR：化学环境有差异的原子核

Crystal Pharmatech
您的药物晶型研究和固态研发专家



典型固体^{13}C核磁谱





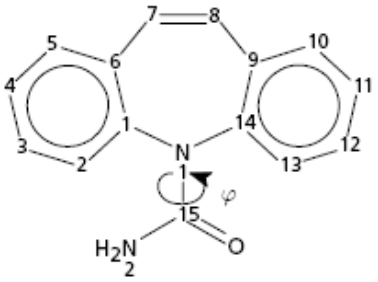
1、**什么核种的谱**：质量数元素名称，如^{13}C、^{19}F、^{15}N、^{31}P

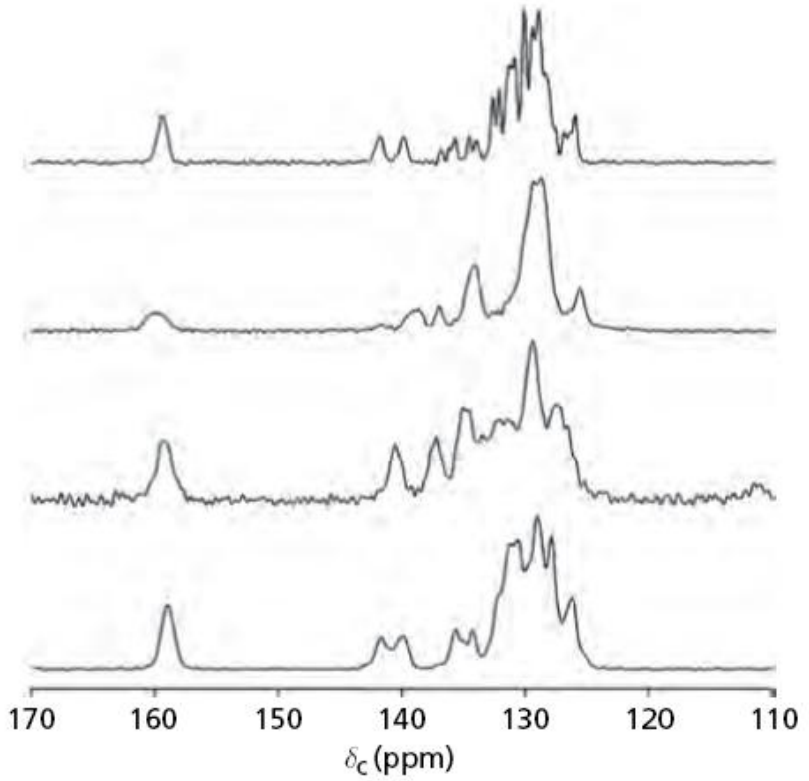
2、**化学位移**：每个峰代表一种原子核所处化学环境

3、**多维谱**：相关代表原子核间有关系

（一） API固态存在形式定性分析
指纹谱比对

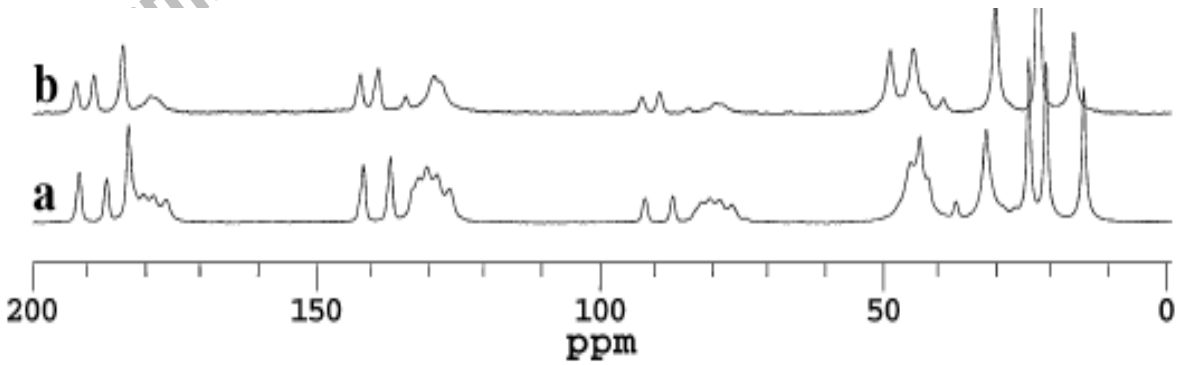
晶型差异

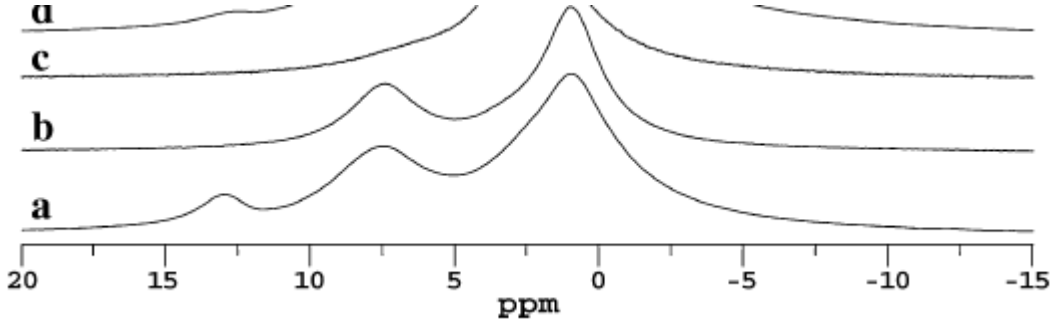




不同晶型卡马西平药物晶体的^{13}C CP/MAS谱

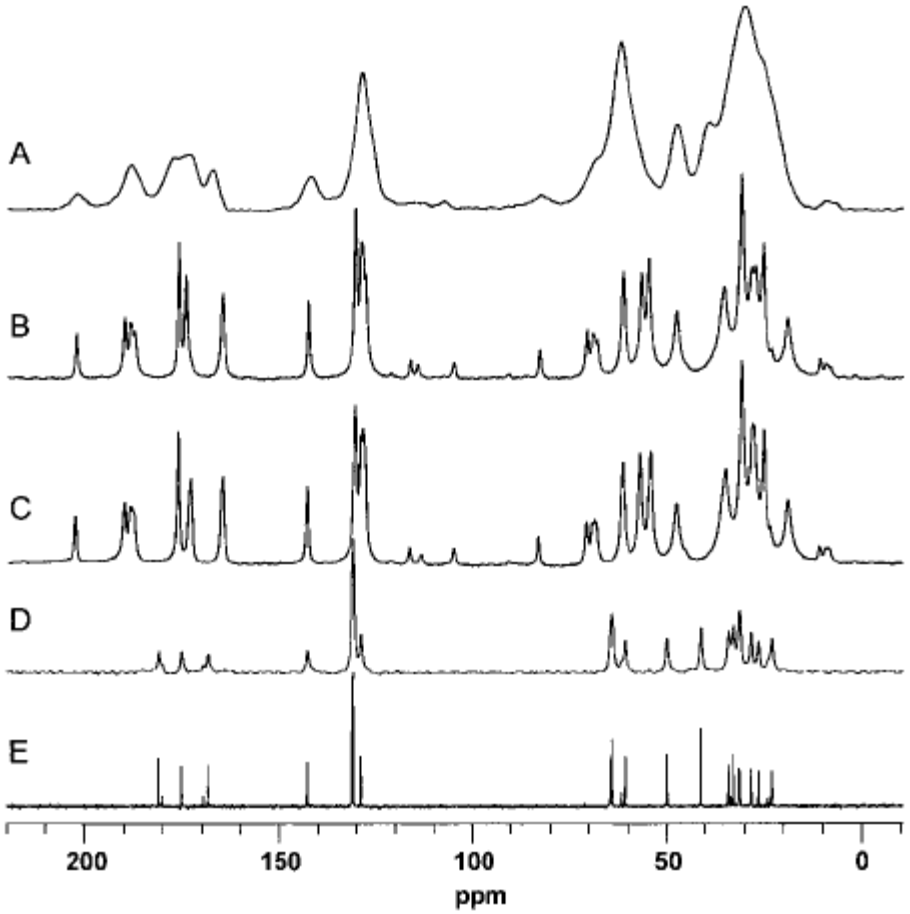
盐和酸





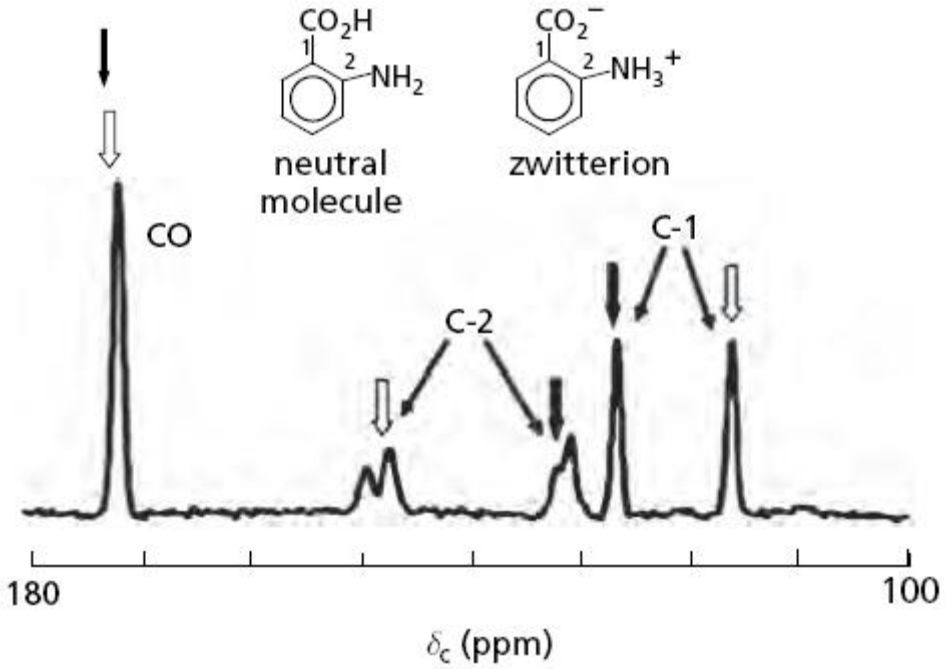
布洛芬酸型和Na盐型药物的^{1}H和^{13}C谱

含结晶水



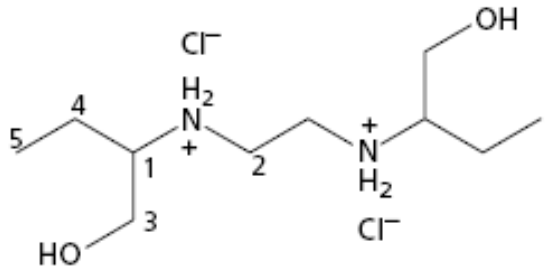
赖诺普利不同条件下^{13}C谱

构相差异

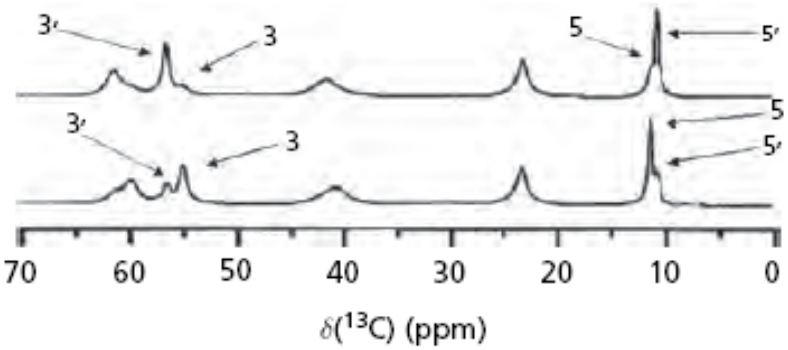


氨基苯酸的^{13}C谱

保存不当：晶型变化



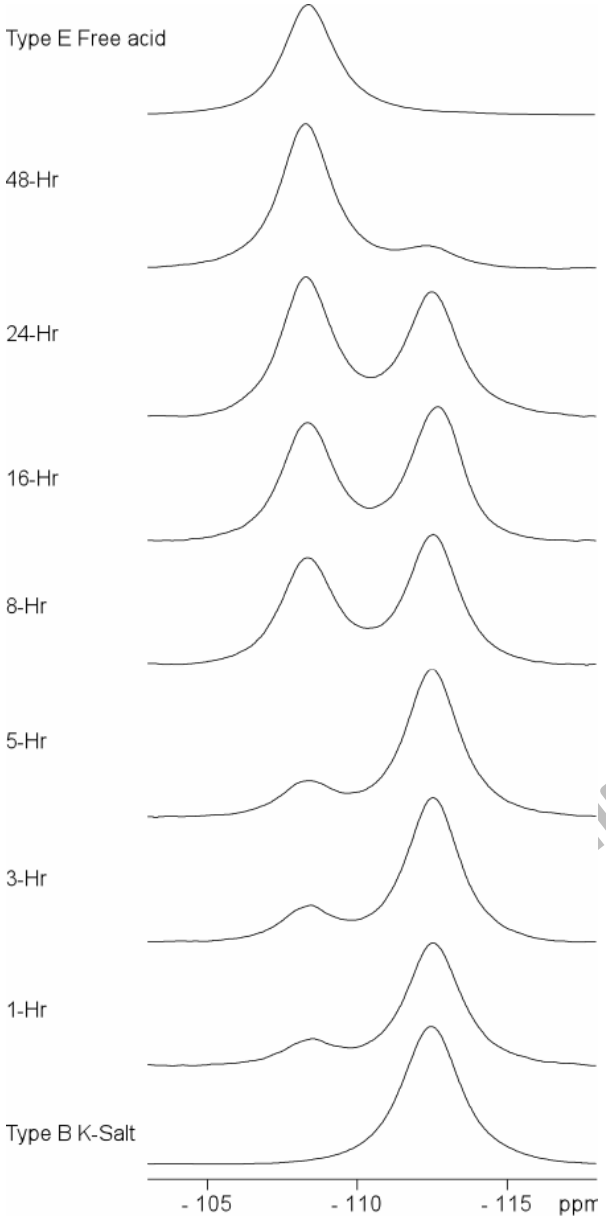
[S,S]Ethambutol hydrochloride (**IV**)



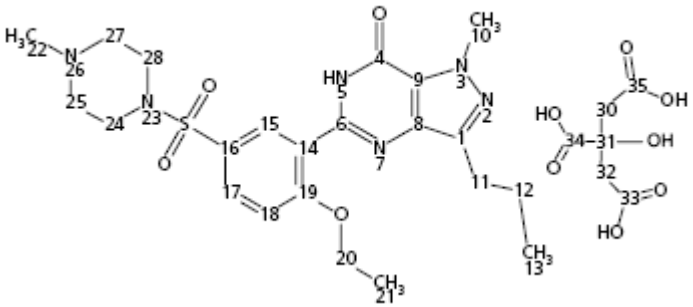
盐酸乙胺丁醇的^{13}C谱

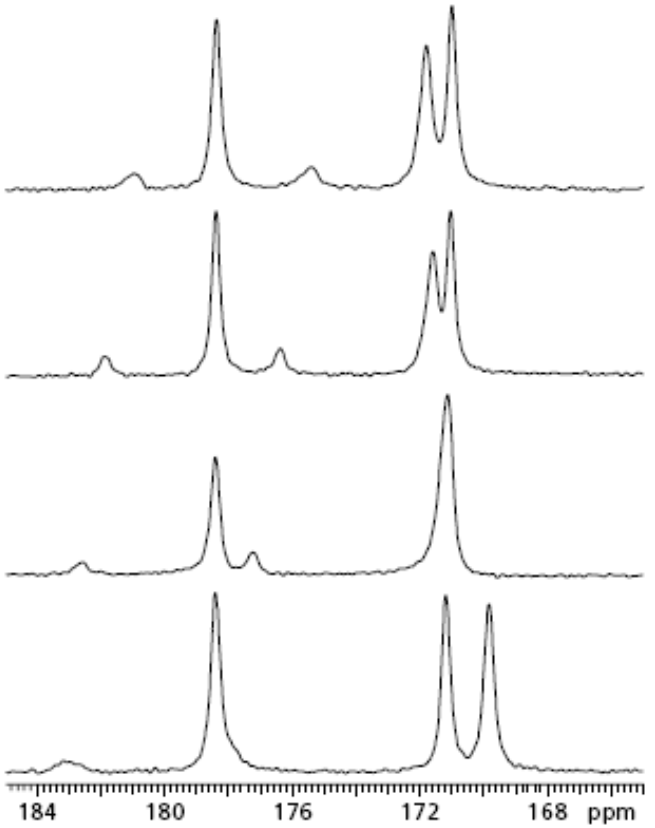
制浆过程：盐岐化

^{19}F MAS NMR



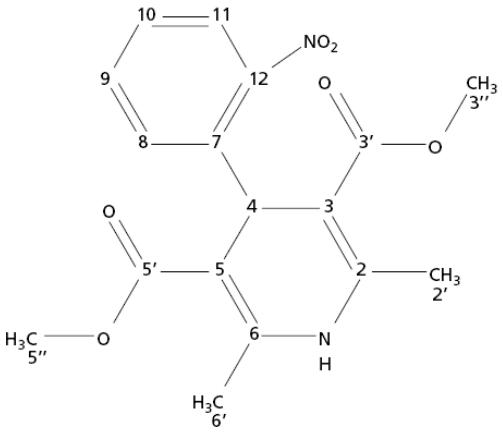
保存过程的变化：湿度影响

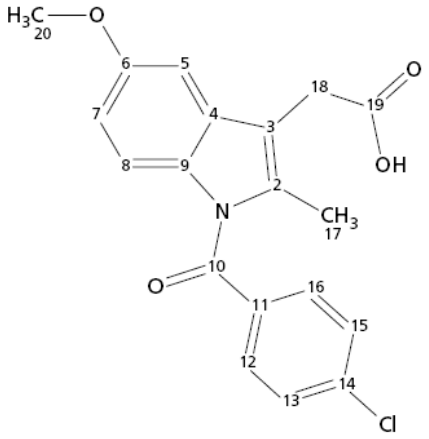


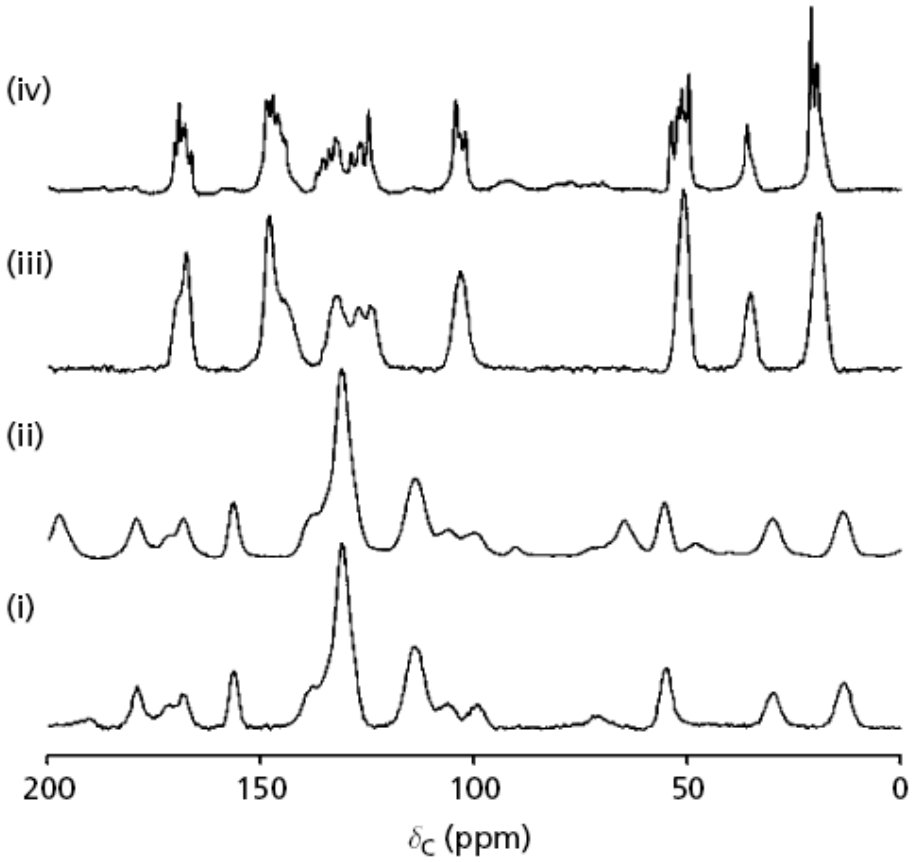


西地那非不同保存条件下^{13}C谱

加工过程的影响







无定型吲哚美辛和硝苯地平加工前后^{13}C谱

检测限

Table 1. Tablets and Capsules of Drugs Investigated in Our Laboratory by Solid-State ^{13}C-NMR Spectroscopy

Drug	Dose (mg)	Total Weight of Dosage Form (mg)	Manufacturer and Trade Name	Number of NMR Scans (# of Scans for Interrupted Decoupling Experiment)
Enalapril maleate	1.25	230	Merck (Vasotec)	16,000 (33,576)
	2.5	230	Merck (Vasotec)	16,000 (33,576)
	5	230	Merck (Vasotec)	16,000 (33,576)
	20	200	Merck (Vasotec)	16,000 (33,576)
Lovastatin	20	400	Merck (Mevacor)	4000 (4000)
Simvastatin	40	400	Merck (Zocor)	4000 (4000)
Ibuprofen tablets	200	320	Bristol-Myers Squibb (Nuprin)	2000 (4048)
	200	330	Upjohn (Haltran)	7264 (2692)
	400	620	Geneva Generics	6000 (9084)
Sulindac tablets	200	330	Merck (Clinoril)	3000 (8104)
Flurbiprofen tablets	100	420	Upjohn (Ansaid)	4000 (10,000)
Diflunisal tablets	500	840	Merck, (Dolobid)	10,000 (20,492)
Indomethacin capsules	50	350	Merck (Indocin)	12,000 (20,000)
	75	280	Merck (Indocin-SR)	12,000 (28,248)
	50	380	Geneva Generics	10,000 (27,772)
	50	480	United Research Laboratories	10,000 (30,000)
Mefenamic acid capsules	250	350	Parke-Davis (Ponstel)	7000 (6000)
Piroxicam capsules	20	300	Pfizer (Feldene)	14,000 (19,556)

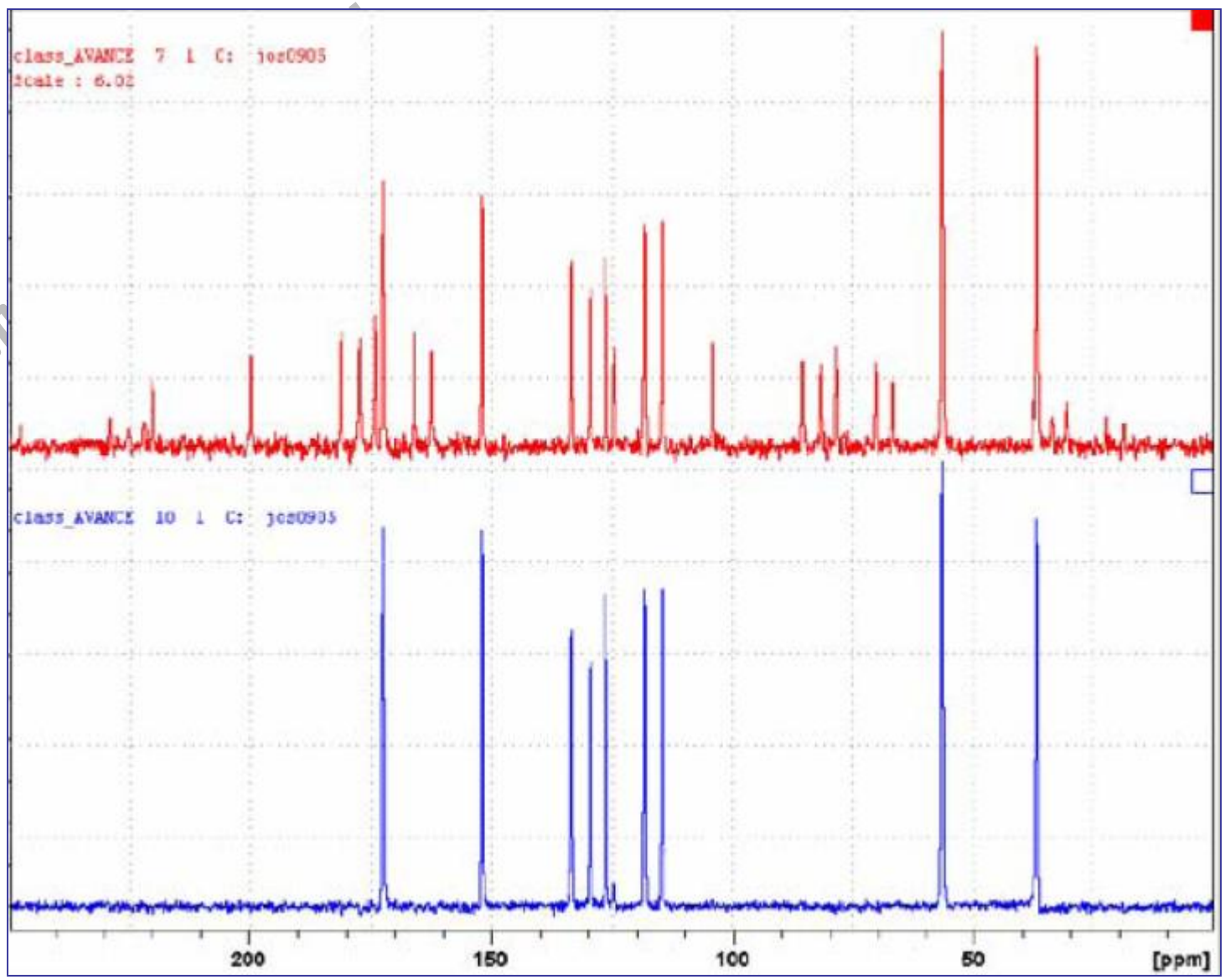
信号强度；信噪比；分辨率

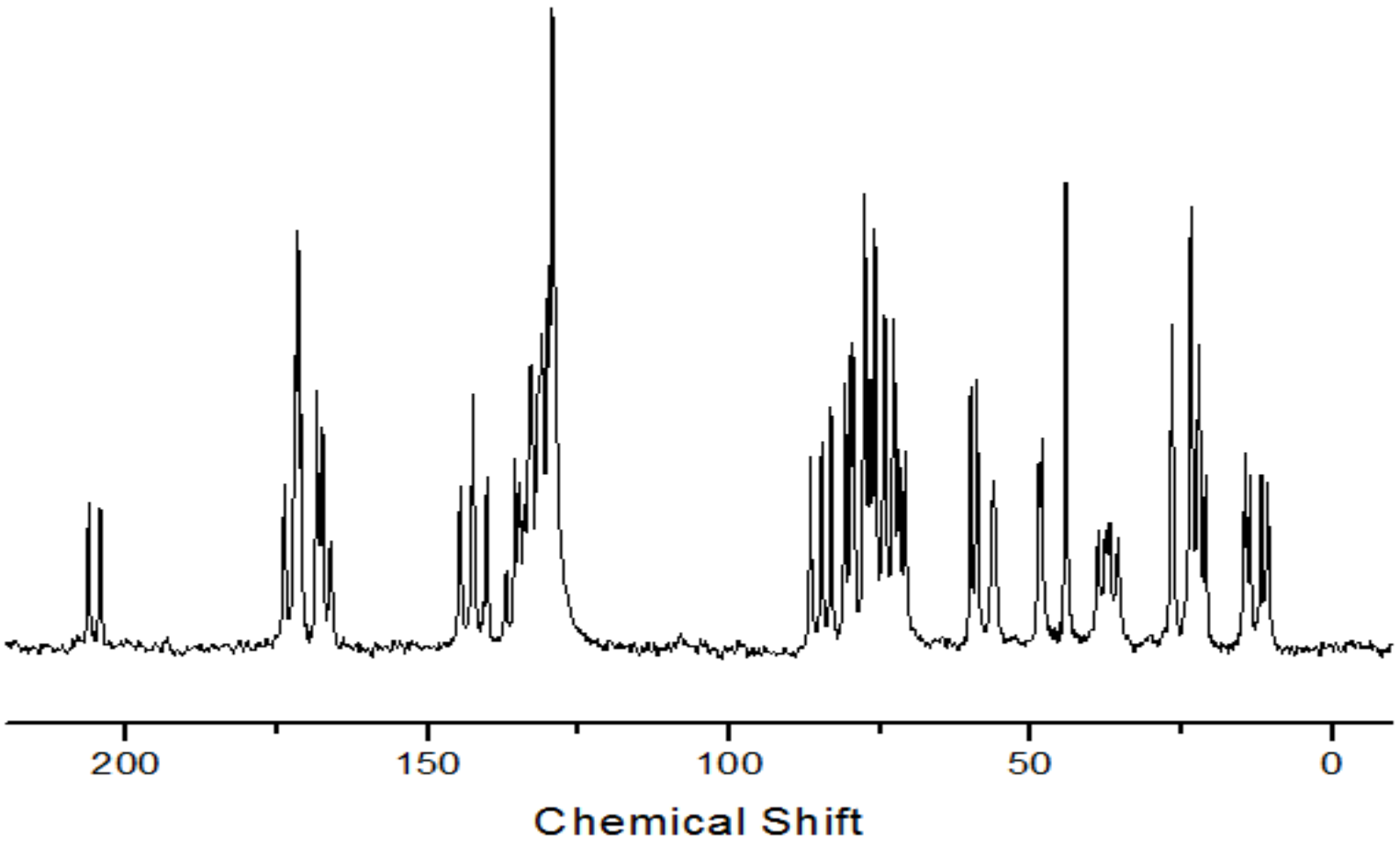
$$M_0 = \frac{N\gamma^2\hbar^2 I(I+1)B_0}{3kT}$$

S/N正比于$\gamma^3 B_0^2$

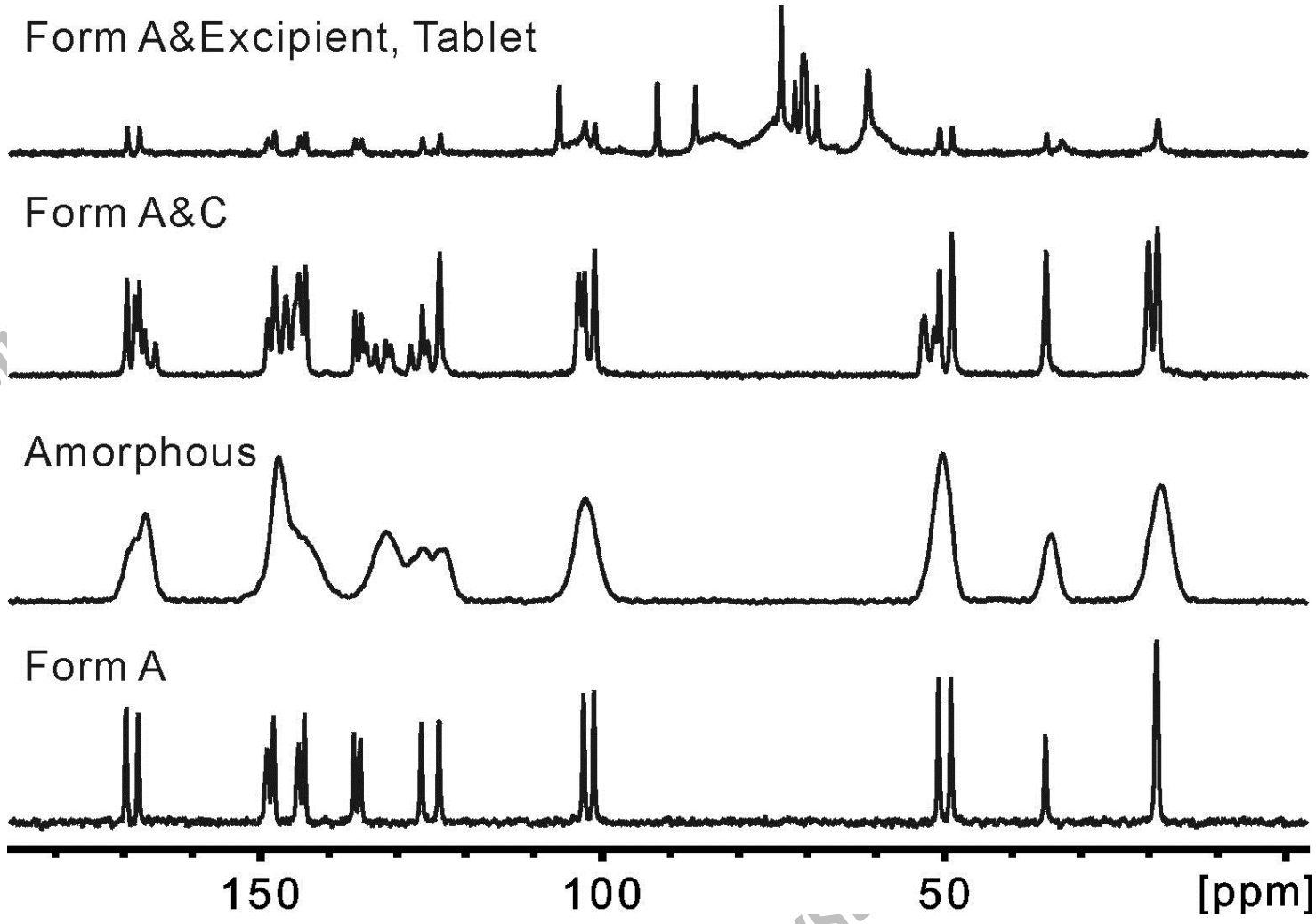
$$H_D = \sum \frac{1}{2}\gamma_i\gamma_j\hbar^2 r^{-3}(\vec{I}_i \cdot \vec{I}_j - 3I_{iz}I_{jz})(3\cos^2\theta_{ij} - 1)$$

核种	天然丰度	磁旋比	I	评价	策略
^{1}H	99.95%	26.752	1/2	信号强 谱峰过宽	高分辨方法
^{19}F	100%	25.168	1/2		
^{13}C	1.108%	6.727	1/2	天然丰度低	交叉极化 非定量
^{15}N	0.365%	-2.711	1/2		
^{23}Na	100%	7.0763	3/2	还不错	
^{31}P	100%	10.829	1/2	很好	


class_AVANCE 7 1 C: jcs0905
2cale : 6.02
class_AVANCE 10 1 C: jcs0905
200
150
100
50
[ppm]

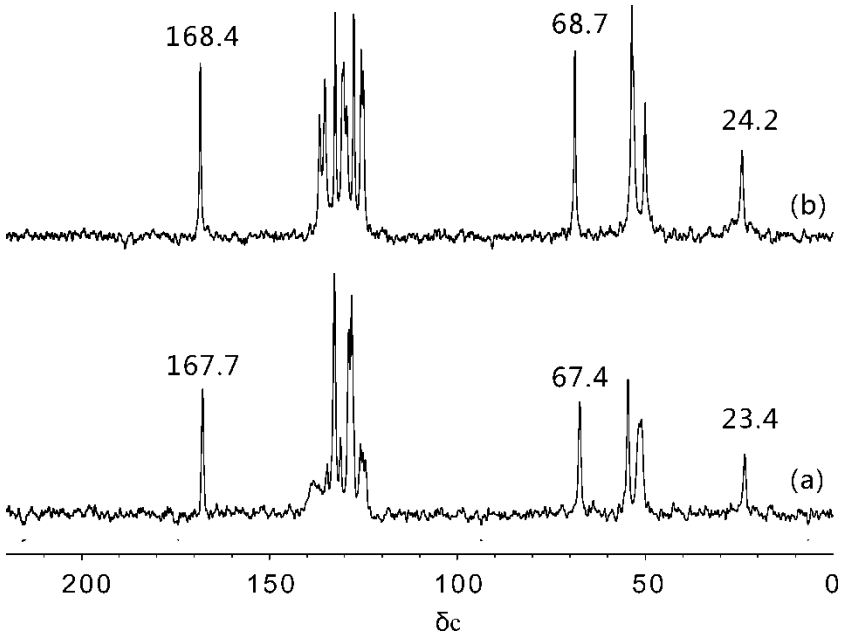


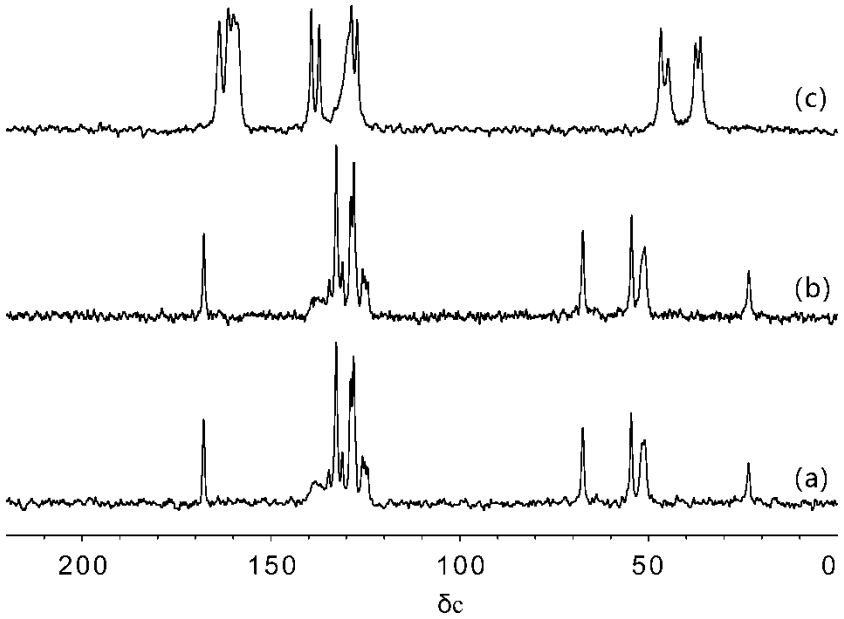
紫杉醇晶体^{13}C CP/MAS TOSS谱

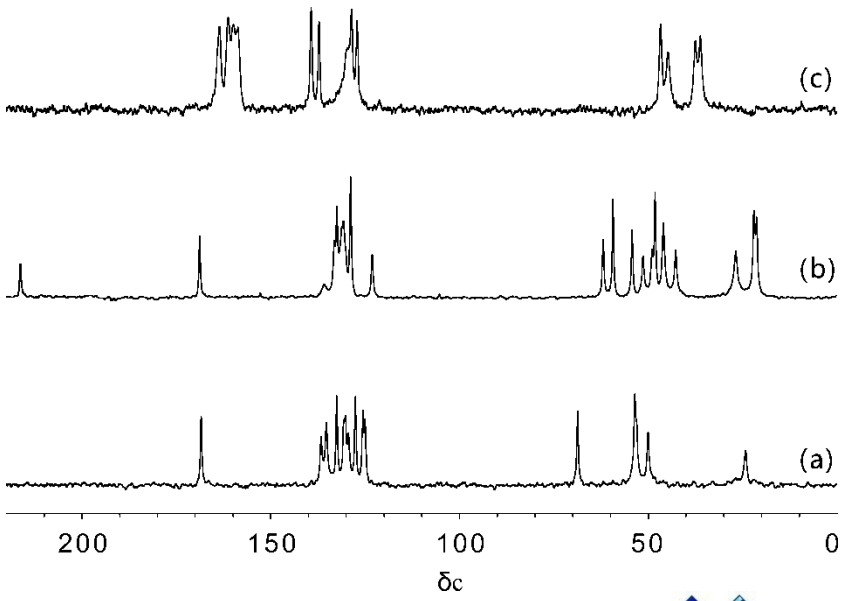


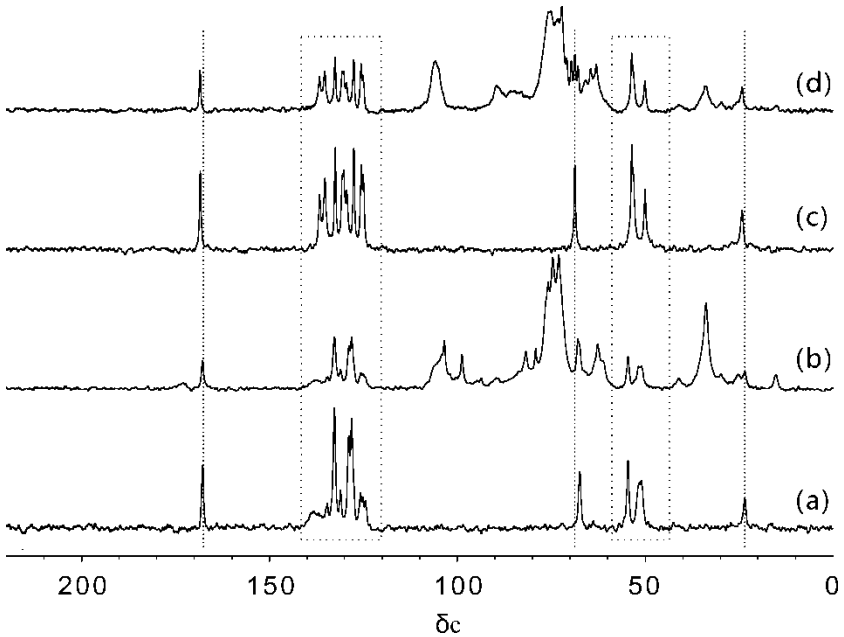
非洛地平 ^{13}C CP/MAS TOSS谱

不同晶型，晶型和无定型差别


168.4
68.7
24.2
(b)
167.7
67.4
23.4
(a)
200
150
100
50
0
δc

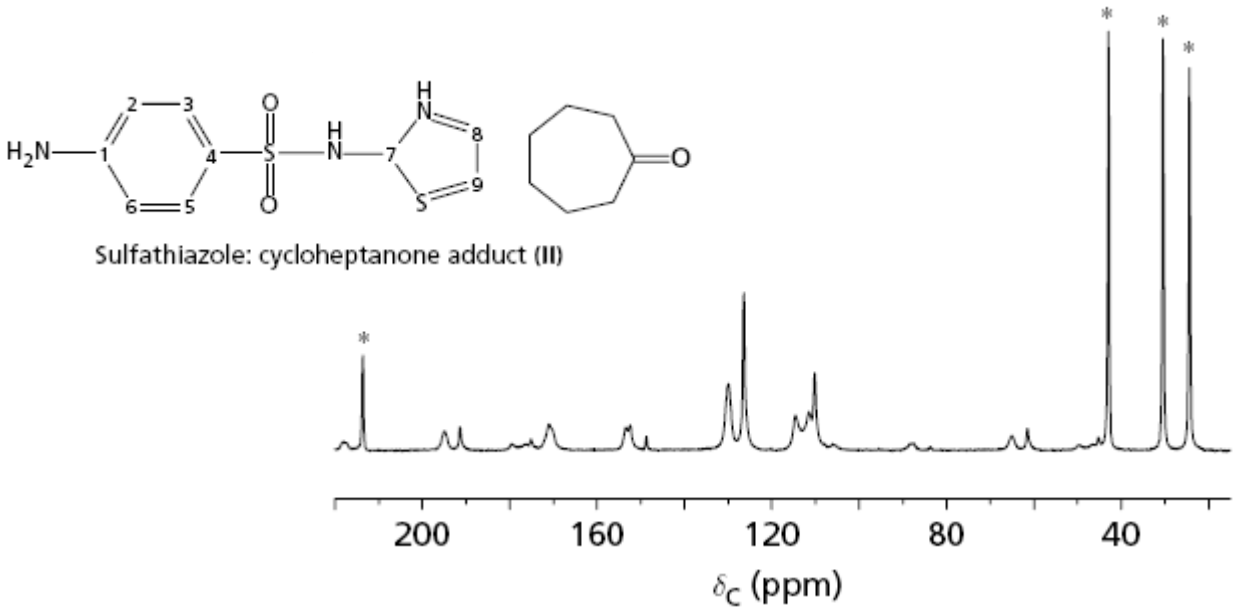

(c)
(b)
(a)
200
150
100
50
0
δc


(c)
(b)
(a)
200
150
100
50
0
δc


(d)
(c)
(b)
(a)
200
150
100
50
0
δc

（二） API溶剂化合物和残余溶剂的区别

溶剂化合物



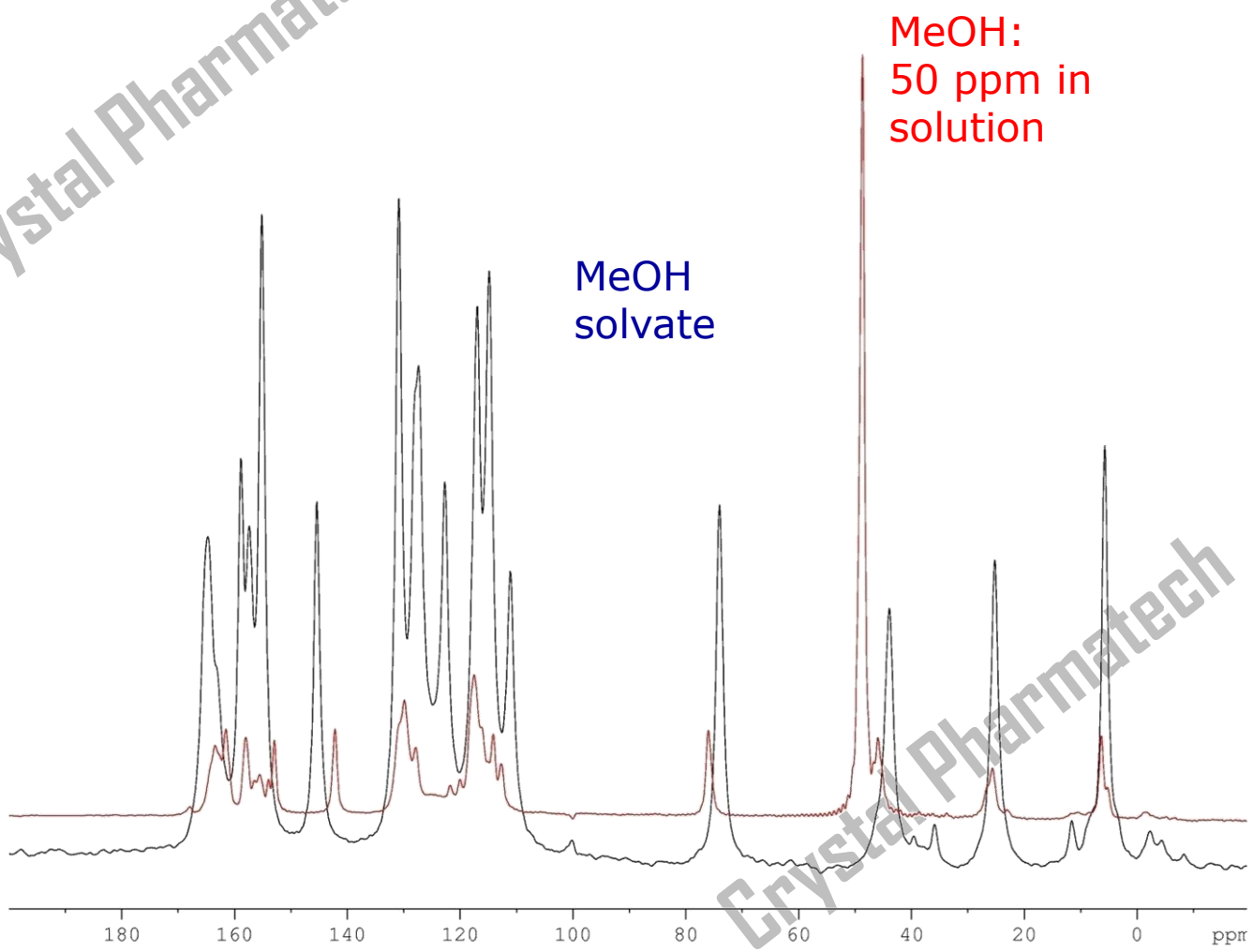
环庚酮溶剂化的磺胺塞唑^{13}C谱

如何区别是残余溶剂还是溶剂化合物？

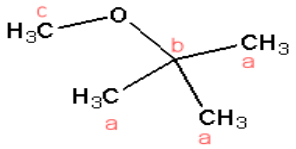
1、自由的残余溶剂和进入晶格的溶剂化学位移有差异

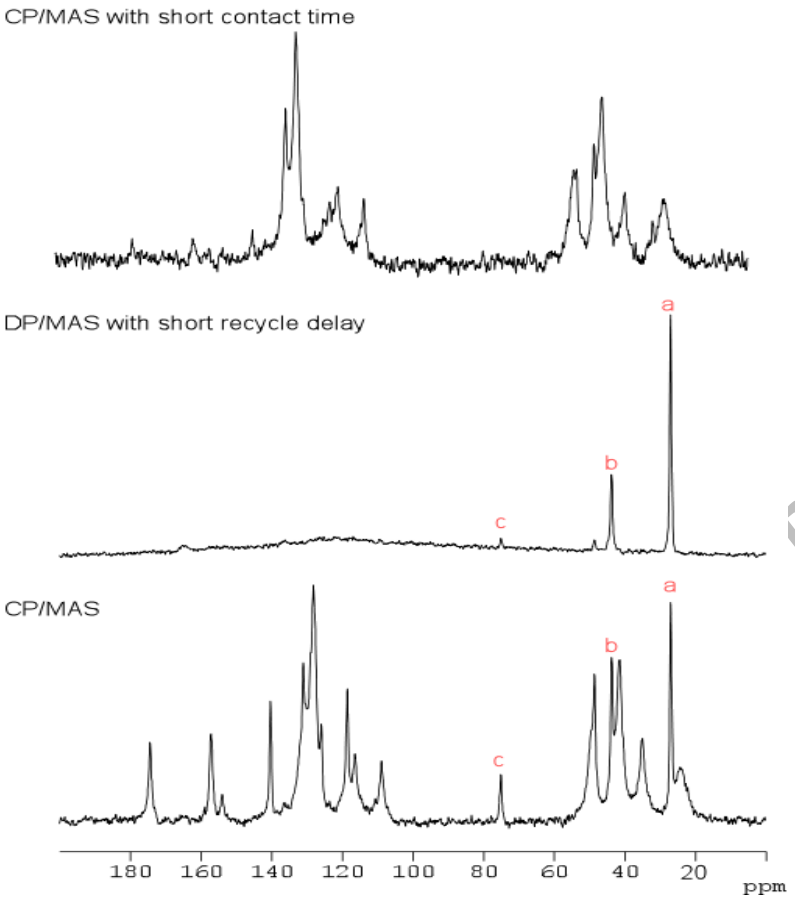
2、自由的残余溶剂和进入晶格的溶剂运动状态有差异

3、溶剂化合物和非溶剂化合物结构有差异

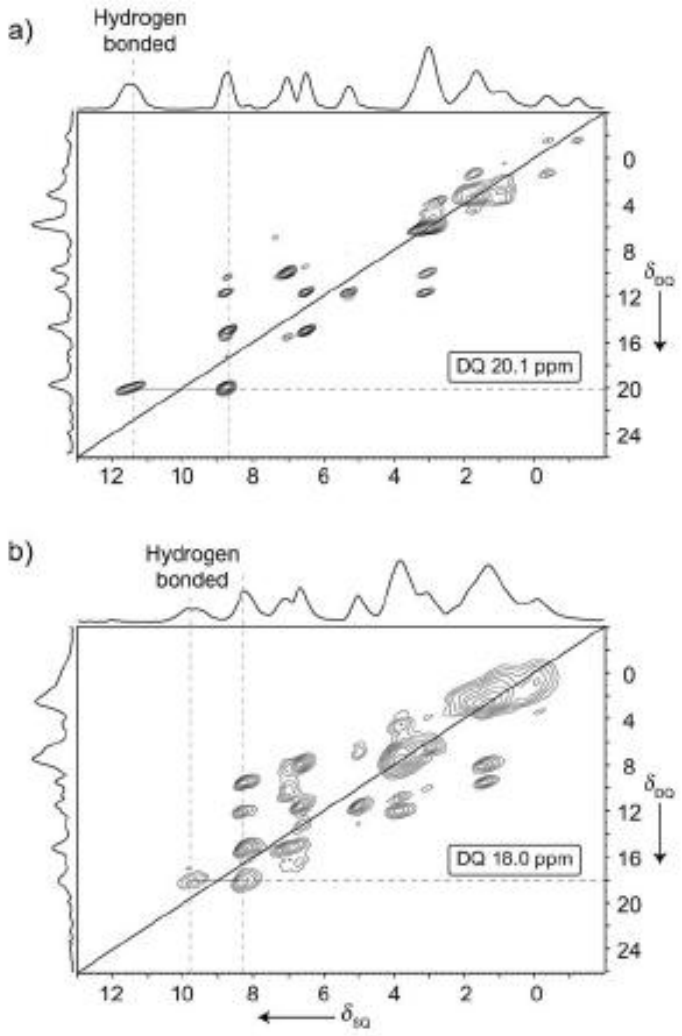


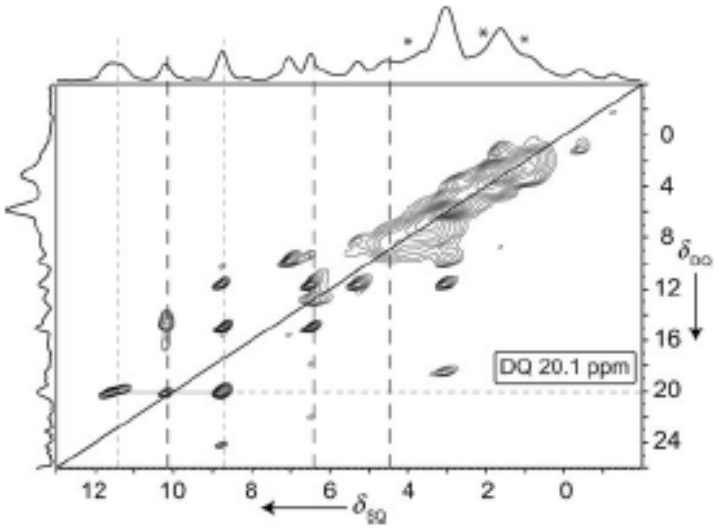
变接触时间CP/MAS





水合物和溶剂化学物鉴定的二维谱方法

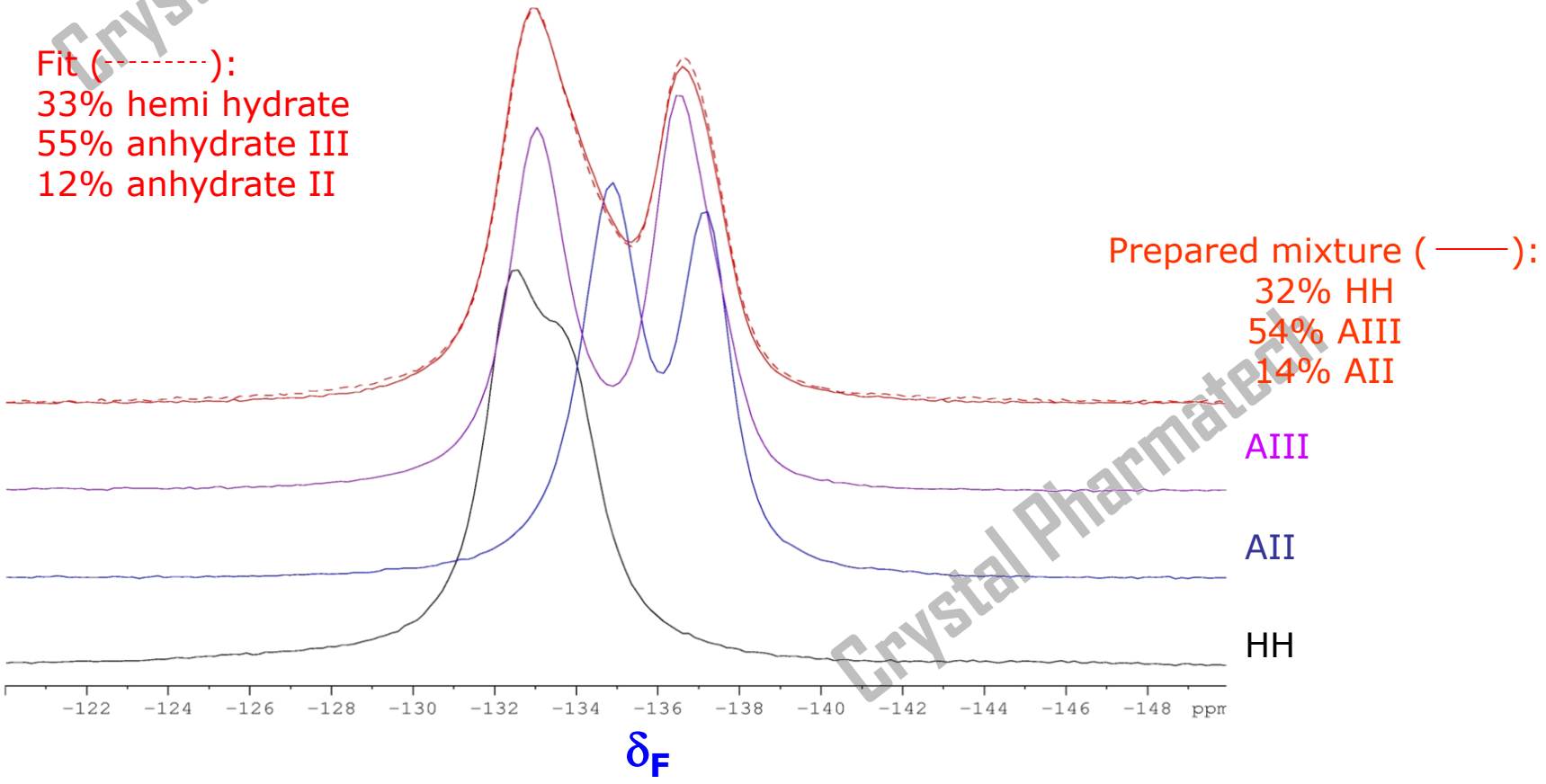




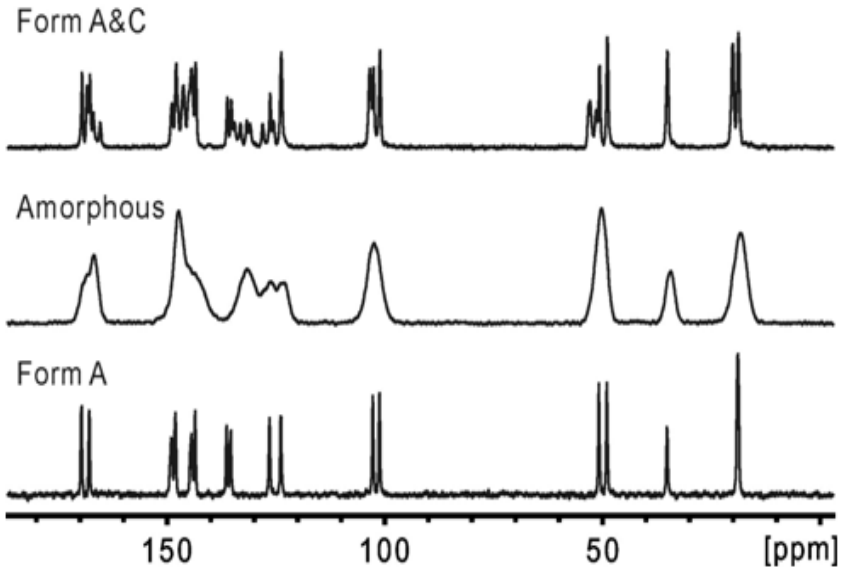
^{1}H-^{1}H DQ SQ NMR

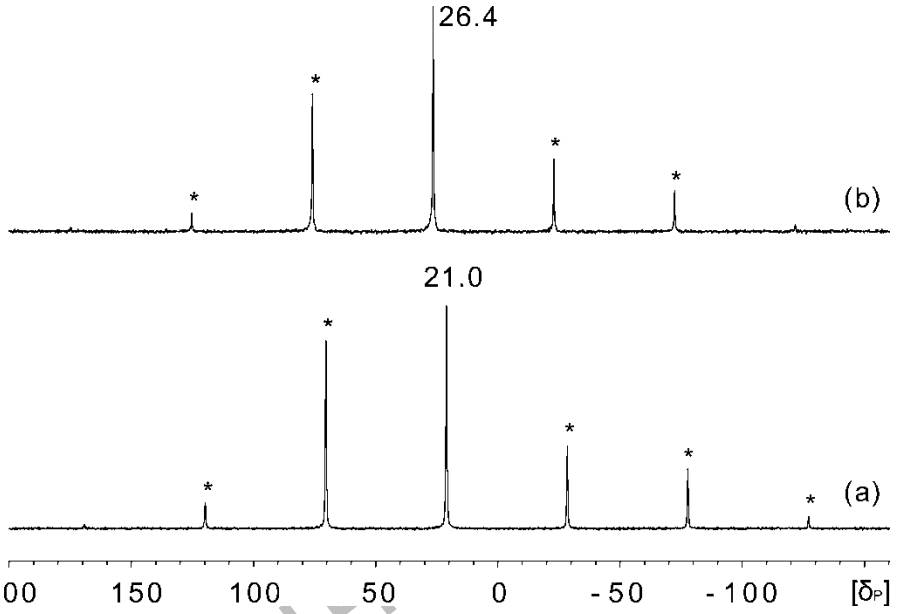
(三) 多固态共存体系的定量

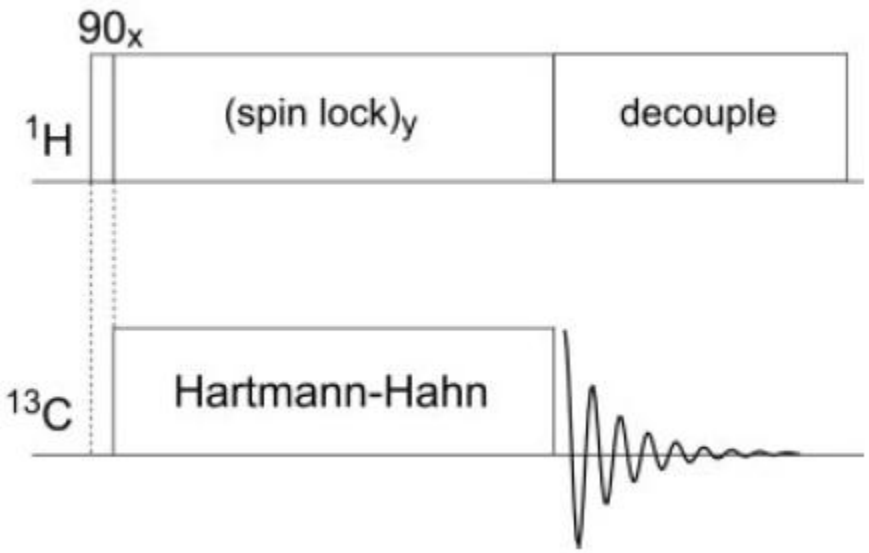
一、基于定量谱的分峰拟合
（脉冲延迟足够的单脉冲谱，^{19}F、^{23}Na、^{31}P）

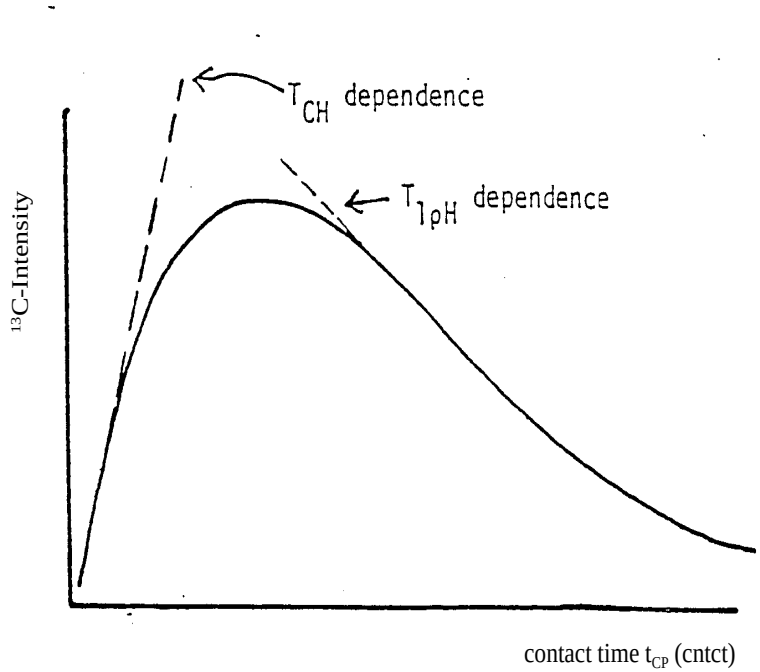


二、基于具有特征峰的非定量谱的CP动力学校准和标准曲线法（脉冲延迟不够的单脉冲谱，交叉极化谱，高分辨谱）







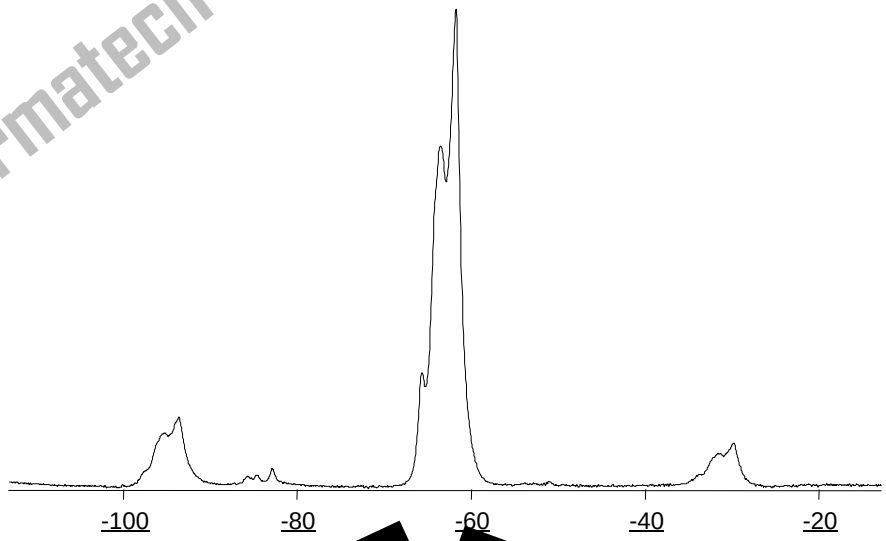


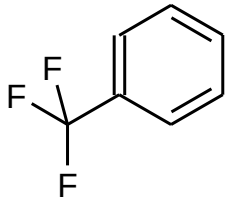
$$I(\tau) = \frac{M^0\left(\frac{\gamma_H}{\gamma_C}\right)\left[\exp\left(-\frac{\tau}{T_{1\rho H}}\right) - \exp\left(-\frac{\tau}{T_{CH}}\right)\right]}{1 - \frac{T_{CH}}{T_{1\rho H}}}$$

$$\frac{M_A^0}{M_B^0} = \frac{\left(1 - \frac{T_{CH}^A}{T_{1\rho H}^A}\right)\left[\exp\left(-\frac{\tau}{T_{1\rho H}^B}\right) - \exp\left(-\frac{\tau}{T_{CH}^B}\right)\right]}{\left(1 - \frac{T_{CH}^B}{T_{1\rho H}^B}\right)\left[\exp\left(-\frac{\tau}{T_{1\rho H}^A}\right) - \exp\left(-\frac{\tau}{T_{CH}^A}\right)\right]} \frac{I_A(\tau)}{I_B(\tau)}$$

$$= F_{A/B} \frac{I_A(\tau)}{I_B(\tau)}$$

三、特征峰重叠的、无标样参照体系的定量





Component 1

39msec T1rho

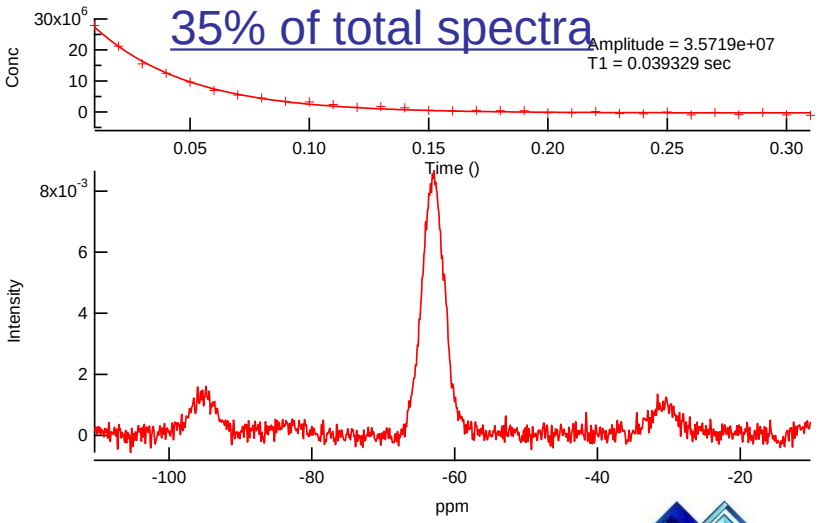
35% of total spectra

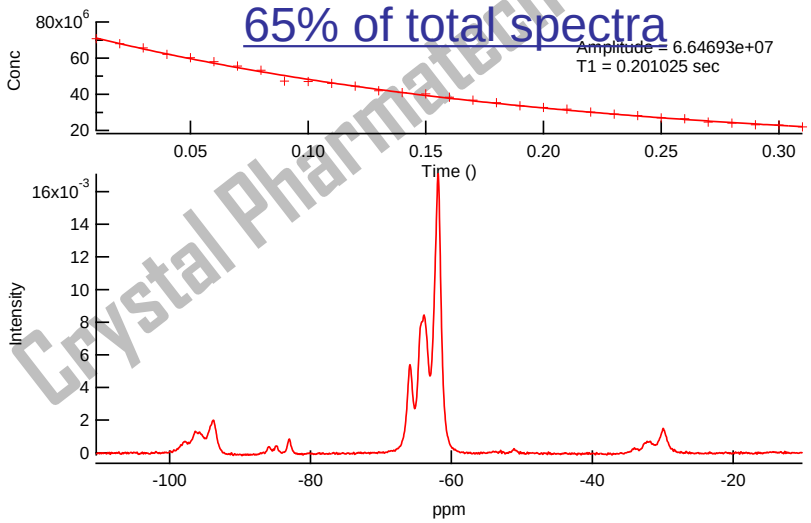
DECRA

Component 2

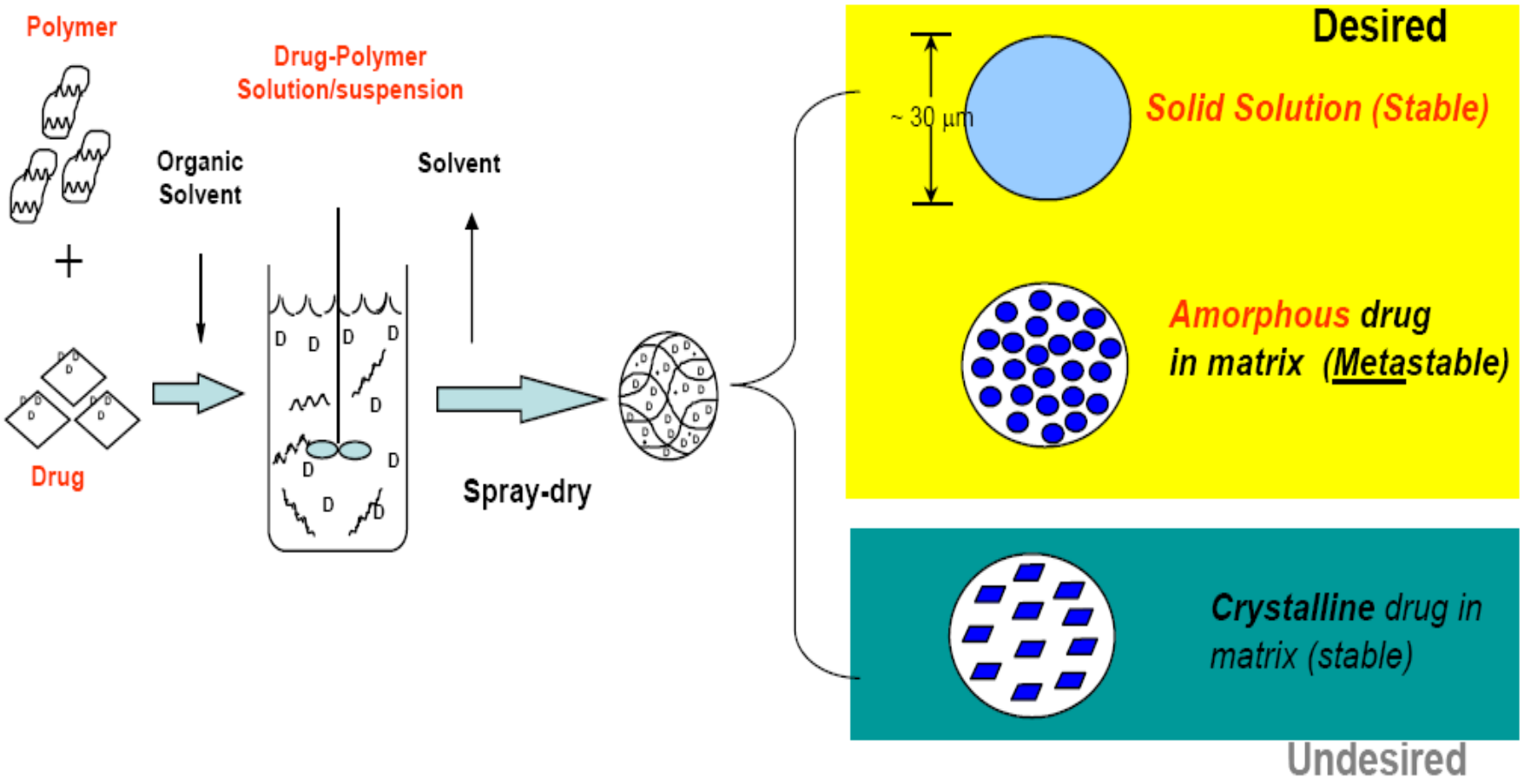
200msec T1rho

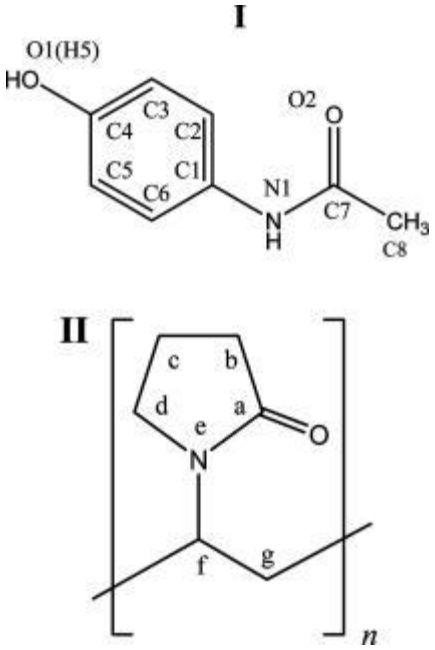
65% of total spectra

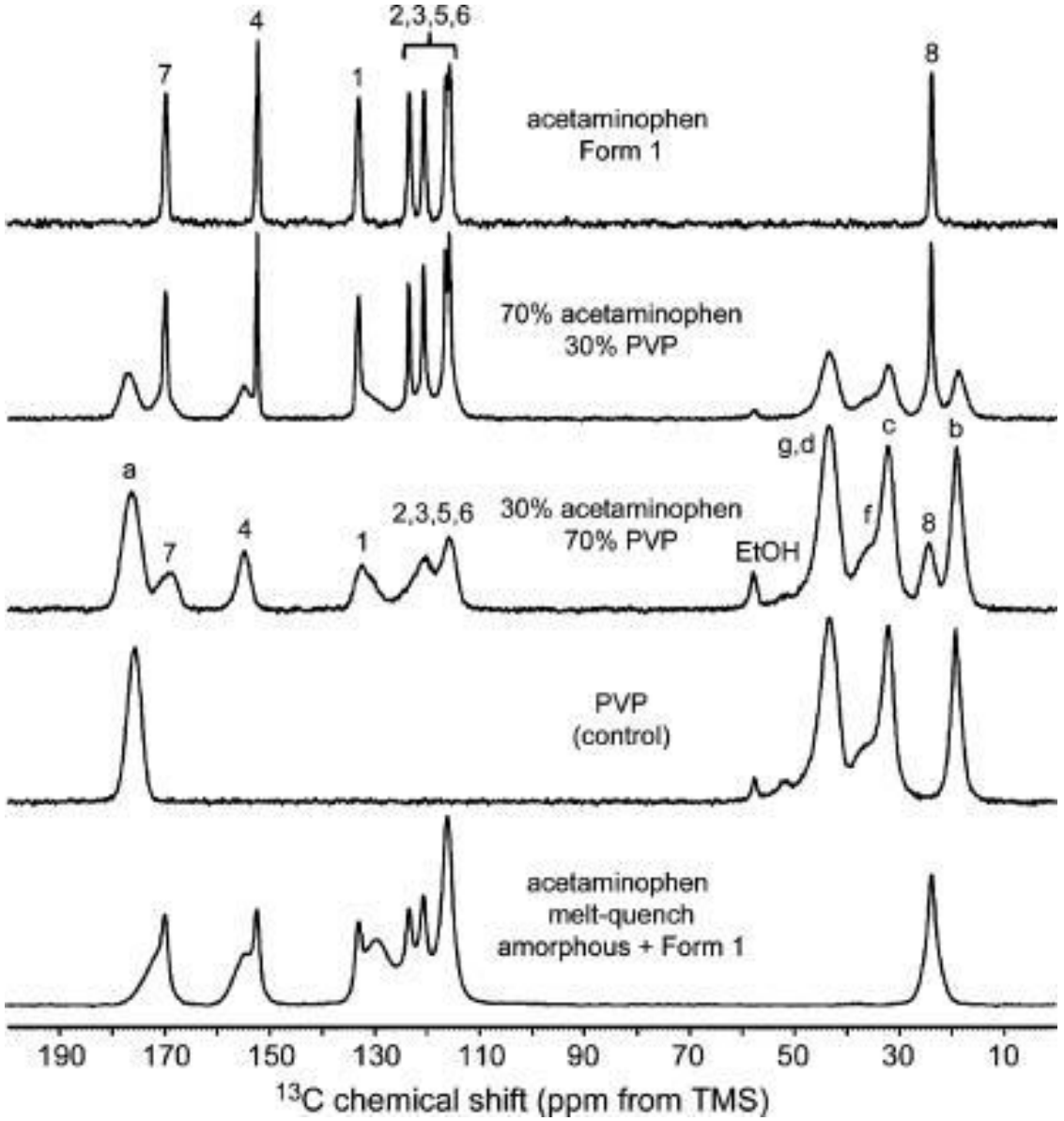


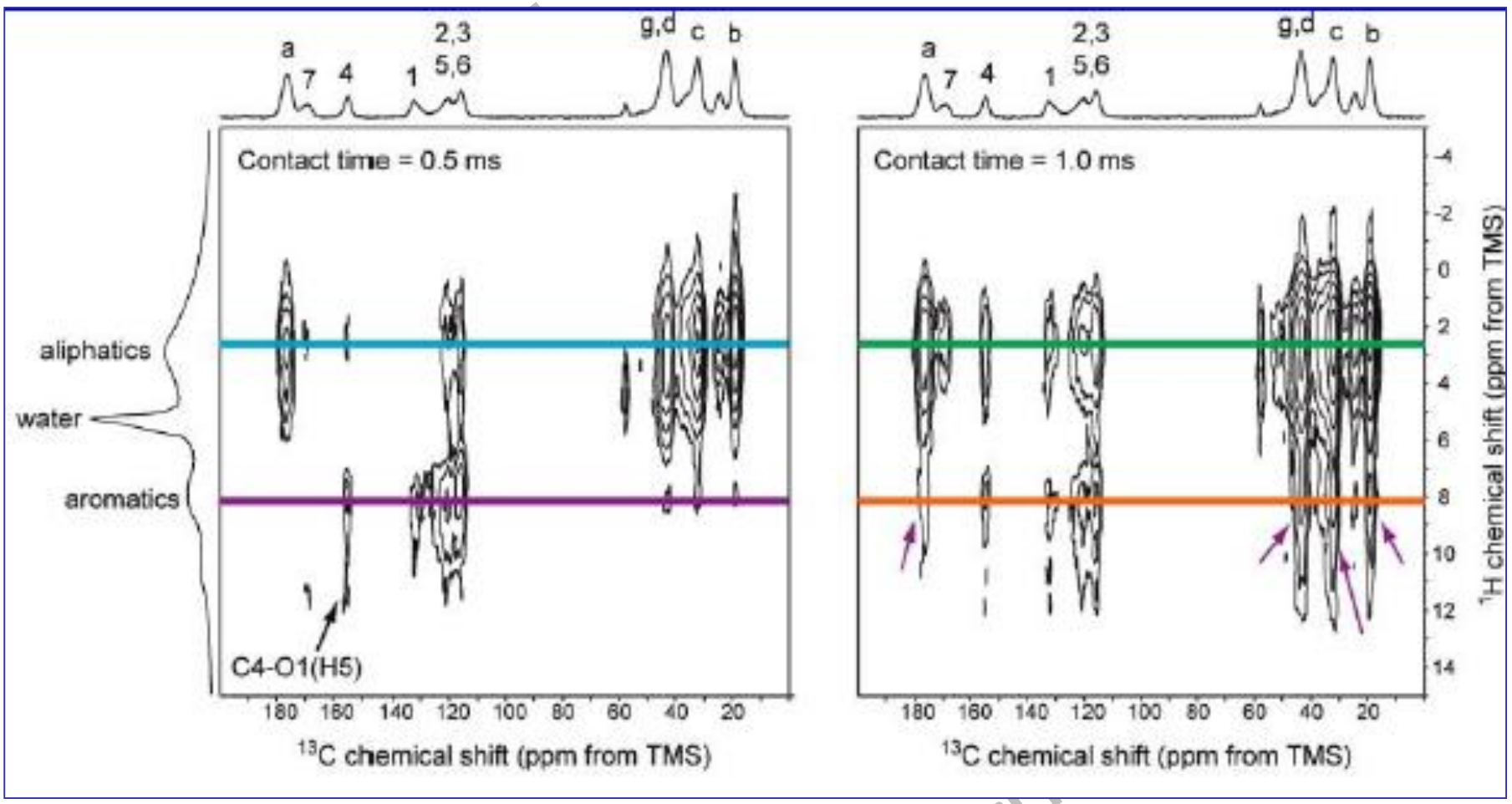


（四）药物无定型分散增溶体系分子水平分散确认


Polymer
Drug-Polymer
Solution/suspension
Organic
Solvent
Solvent
Drug
Spray-dry
Desired
~ 30 µm
Solid Solution (Stable)
Amorphous drug
in matrix (Metastable)
Crystalline drug in
matrix (stable)
Undesired


I
O1(H5)
HO
C3
C4
C2
C5
C1
C6
O2
O
N1
N
H
C7
CH3
C8
II
c
b
d
a
e
N
O
f
g
n


4
2,3,5,6
7
1
8
acetaminophen
Form 1
70% acetaminophen
30% PVP
g,d
c
b
a
2,3,5,6
30% acetaminophen
70% PVP
7
4
1
EtOH
f
8
PVP
(control)
acetaminophen
melt-quench
amorphous + Form 1
190
170
150
130
110
90
70
50
30
10
13C chemical shift (ppm from TMS)

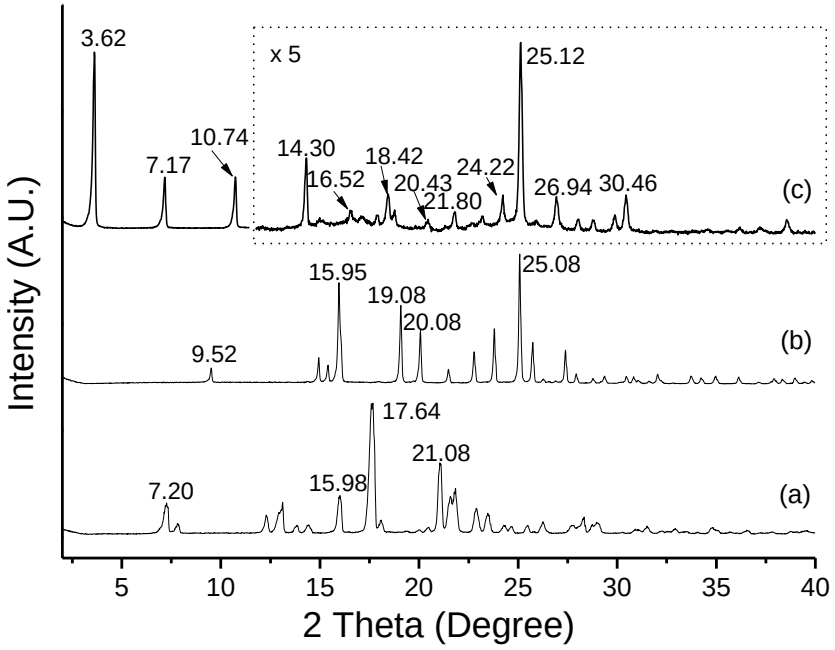


分子间信号相关的出现，说明两种分子大量的在分子尺度临近

assignment	δ (ppm)	$\Delta\delta_l^b$ (ppm)	$\Delta\delta_a^c$ (ppm)	T_1^d (s)
7	169.4	−0.4	−2.0	3.74 ± 0.28
4	154.9	2.5	0.6	3.64 ± 0.13
1	132.2	−0.9	2.8	3.97 ± 0.21
3, 5	120.3			4.00 ± 0.2
2, 6	115.7	0.0	−0.1	3.35 ± 0.10
8	24.6	0.7	0.8	3.95 ± 0.17
PVP (a)	176.4			3.60 ± 0.06
PVP (g, d)	43.3			3.60 ± 0.05
PVP (f)	36.0			3.98 ± 0.19
PVP (c)	32.2			3.60 ± 0.04
PVP (b)	19.1			3.54 ± 0.05
average				
I				3.8 ± 0.3[e]
PVP				3.7 ± 0.2[e]

单相的物质具有相同的T1值

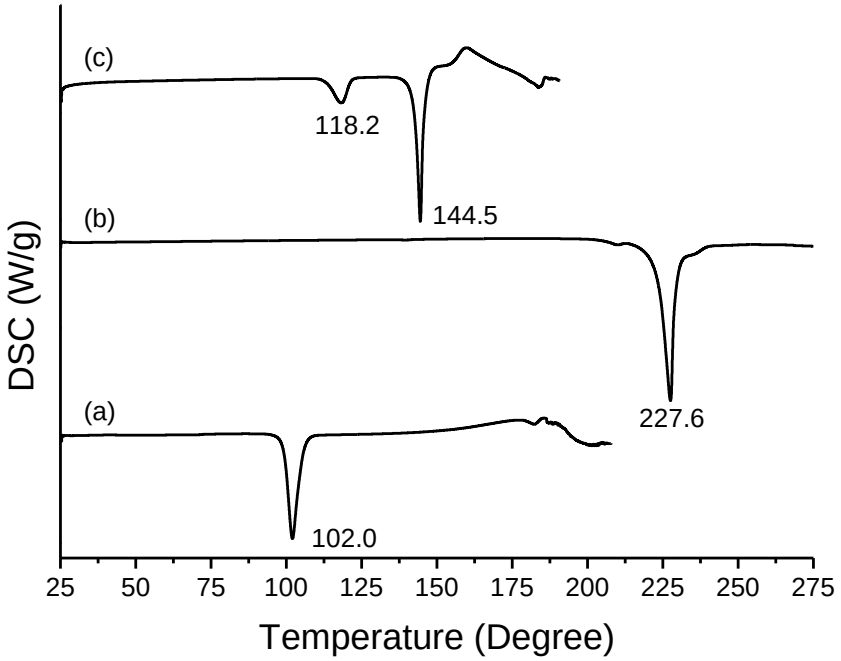
（五）共晶的确认

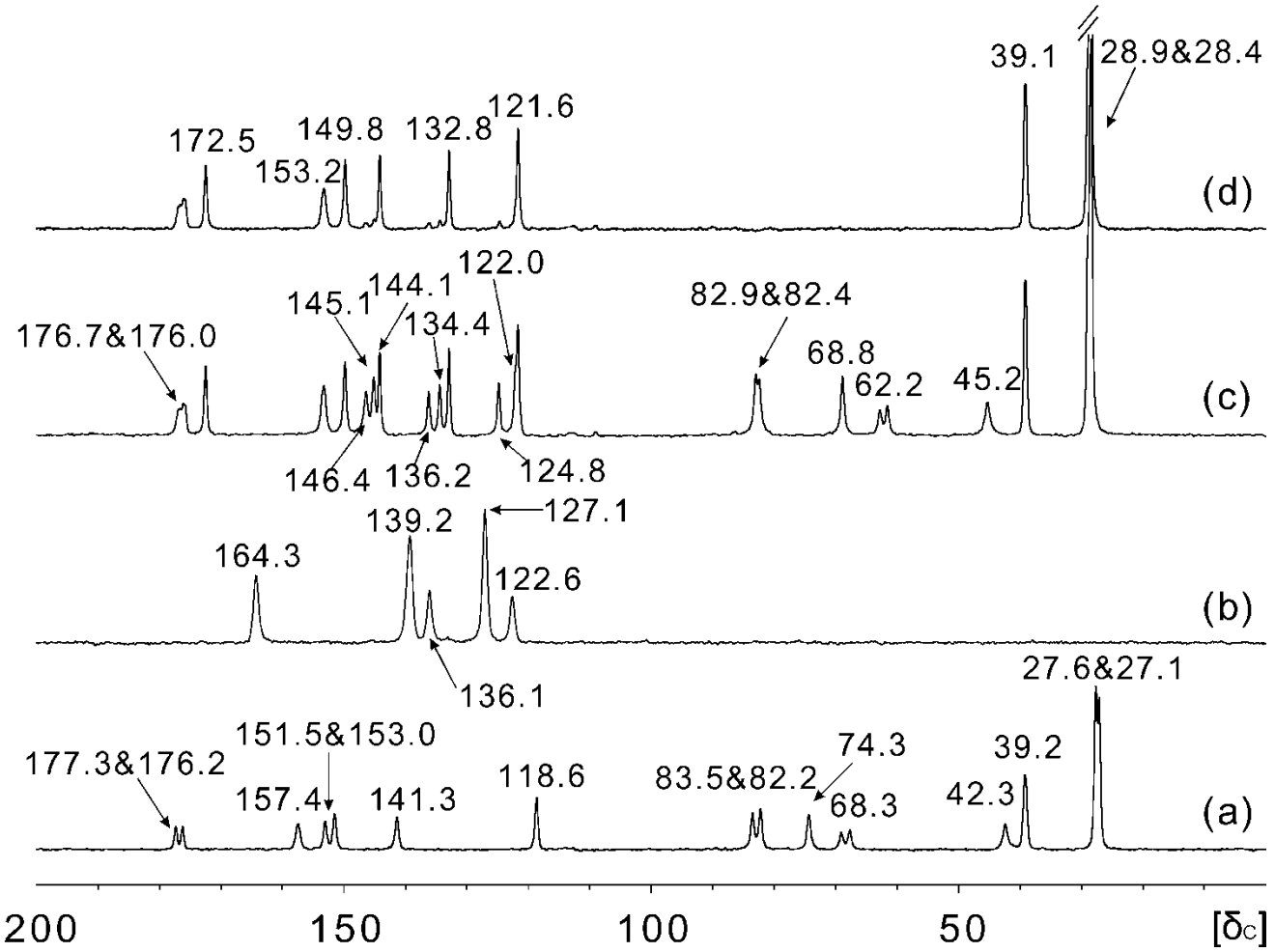


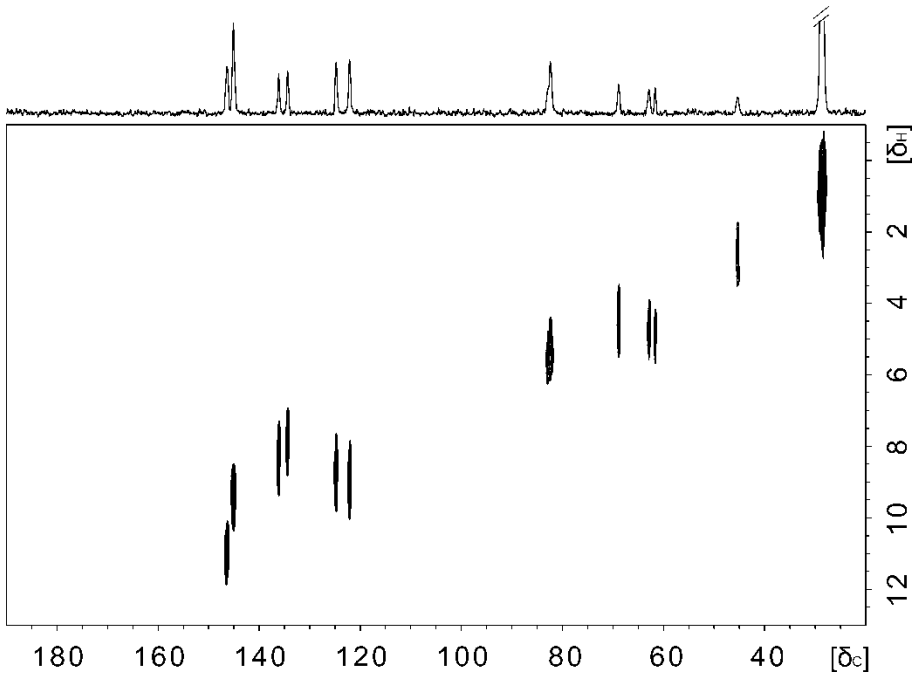
不同于原料的衍射峰出现

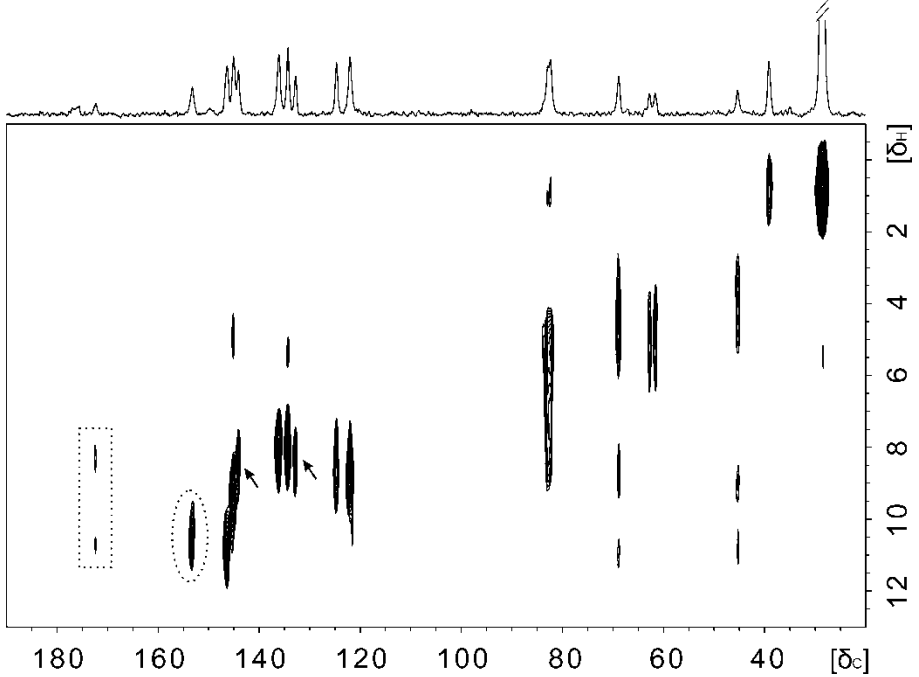
1、新的原料的相

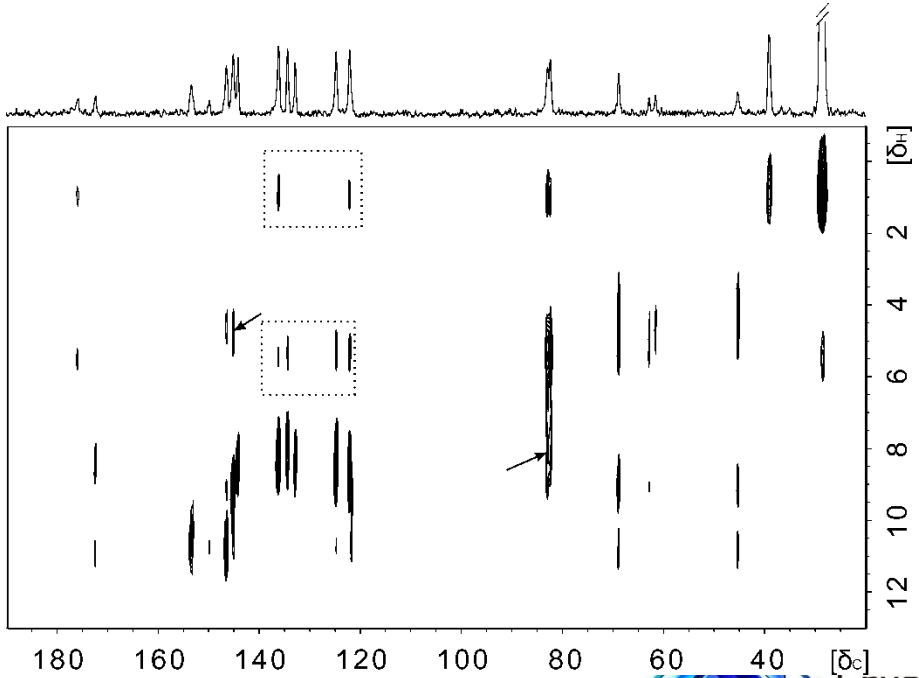
2、不单一的相




39.1
28.9&28.4
172.5
149.8
132.8
121.6
153.2
(d)
122.0
144.1
145.1
82.9&82.4
134.4
176.7&176.0
68.8
62.2
45.2
(c)
146.4
136.2
124.8
139.2
127.1
164.3
122.6
(b)
136.1
27.6&27.1
151.5&153.0
74.3
39.2
177.3&176.2
118.6
83.5&82.2
157.4
141.3
68.3
42.3
(a)
200
150
100
50
[δC]







左上：一键CH相关
右上：二键CH相关
左下：分子间CH相关

assignment	δc	T_1 (s)	assignment	δc	T_1 (s)
1	153.2	2.39	21, 22	136.2	2.30
2, 5	145.1	2.42		134.4	2.30
	146.4	2.19	23, 24	124.8	2.25
3	121.6	2.30		122.0	--
4	149.8	2.20	25	132.8	2.31
6	45.2	2.27[a]	26	172.5	2.35
7	68.8	2.31	27	144.1	2.34
8	62.2($^1J_{C\text{-}P}$=155 Hz)	2.30[a]			
9, 10	82.9&82.4	2.47[a]			
11, 12	176.7&176.0	2.33[a]			
13, 14	39.1	2.29			
15-20	28.9&28.4	2.27[a]			
average		2.31	average		2.31

总结

- ssNMR是一种方法复杂的、花样百出的，但在某些问题上具有不可替代性优势的研究型表征手段。
- 在制药领域的应用包括固态存在形式的定性和定量，API和其它相互作用的研究等。
- 定性实验要注意谱图的有效简化，一般使用边带压制技术。
- 定量实验要注意参数必须符合定量条件。
- 高分辨二维相关技术结合弛豫时间测量，是研究药物分散、共晶、溶剂合物的有力手段。

谢谢大家