LECTURE NOTES CHEM 781
PART 7: Coupling constants from COSY experiments November 17, 2008

7.1. Description of NMR experiments by product operators:

7.1.1. Operators for two spin system

The COSY experiment can be fully understood on the basis of the simple vector picture. A more thorough description of NMR experiments can be done by using product operators derived from quantum mechanics. For a two spin system there will be operators involving both one and two spins. The one spin operators which are equivalent to the vectors describing x,y, or z magnetization. One class of two spin operators describes antiphase magnetization which we already introduced in a semiclassical fashion from the vector picture.

For two coupled spins I^A and I^B there is a total of $2^4 = 16$ possible operators:

$I_z^A, I_x^A, I_y^A, I_z^B, I_x^B, I_y^B$	(6)	z, x or y magnetization of spin A or B (same as in vector picture)
$I_x^A I_z^B, I_y^A I_z^B, ...$	(4)	antiphase x magnetization for spin A coupled to spin B
$I_x^A I_y^B, I_x^A I_x^B, ...$	(4)	double and zero quantum coherence of spin A and B
$I_z^A I_z^B$	(1)	longitudinal spin order (population inversion of A relative to B)
1	(1)	unity operator (needed for mathematical reasons)

All interconversions between operators can be regarded as rotations, giving a sine and a cos component:

Initial state · rotation operator = cos component(initial) + sine component(new)

7.1.2 Rules of rotation starting from an initial state:

- each component of a two spin operator can be treated separately
- if initial state is perpendicular to rotation axis, it will change as a cosine, and a new state will emerge perpendicular to rotation axis and initial state with a sine dependence. Sense of rotation given by right hand rule (note that some books use left hand rule).
- If initial state parallel to rotation axis, it will remain unchanged.
- Only the one spin operators (I_z, I_x, I_y) will give rise to an observable

Effect of pulse: rotation about axis of pulse (x or y) by angle θ:

Initial state	rotation ——>	cos component(initial)	sine component(new)
I_z^A	θ_x^A	$I_z \cos\theta$	$-I_y^A \sin\theta$
I_z^B	θ_x^A	I_z^B	-
I_x^A	θ_x^A	I_x^A	-
I_y^A	θ_x^A	$I_y \cos\theta$	$-I_z^A \sin\theta$
$I_x^A I_z^B$	$\theta_y^{A,B}$	$I_x^A I_z^B \cos\theta$	$-I_z^A I_x^B \sin\theta$
$I_y^A I_z^B$	θ_x^A	$I_y^A I_z^B \cos\theta$	$I_z^A I_z^B \sin\theta$
$I_y^A I_z^B$	θ_x^B	$I_y^A I_z^B \cos\theta$	$-I_y^A I_y^B \sin\theta$

Chemical shift: rotation about z axis by angle Ω t

I_z^A	$\Omega^A t$	I_z^A	
I_x^A	$\Omega^A t$	$I_x^A \cos(\Omega t)$	$I_y^A \sin\Omega t$
I_y^A	$\Omega^A t$	$I_y^A \cos(\Omega t)$	$-I_x^A \sin(\Omega t)$
$I_x^A I_z^B$	$\Omega^A t$	$I_x^A I_z^B \cos(\Omega t)$	$I_y^A I_z^B \sin(\Omega t)$
$I_z^A I_y^B$	$\Omega^A t$	$I_z^A I_y^B$	

spin-spin coupling: rotation about $I_z^A I_{,z}^B$ axis: interconversion between in phase x,y and anti phase x,y components by π J t:

I_z^A	$\pi J_{AB} t$	I_z^A	
I_y^A	$\pi J_{AB} t$	$I_y^A \cos(\pi J_{AB} t)$	$-I_x^A I_z^B \sin(\pi J_{AB} t)$
$I_x^A I_z^B$	$\pi J_{AB} t$	$I_x^A I_z^B \cos(\pi J_{AB} t)$	$I_y^A \sin(\pi J_{AB} t)$
$I_z^A I_x^B$	$\pi J_{AB} t$	$I_z^A I_x^B \cos(\pi J_{AB} t)$	$I_y^B \sin(\pi J_{AB} t)$
$I_x^A I_y^B$	$\pi J_{AB} t$	$I_x^A I_y^B$ (DQ-terms do not evolve mutual coupling)	

7.2. Example COSY:

The COSY experiment [$(90°)_x\ t_1\ (90°)_x$ acqu.] contains two pulses and one evolution time t_1 during which both coupling and shift occur. It can be shown that simultaneous coupling and shift can be treated in sequence. Thus the following sequence of four rotations has to be considered:

$$90°_x{}^{A,B} \text{-- } (\Omega^{A,B}\ t_1)_z \text{ --- } (\pi\ J_{AB}\ t_1)_{zz} \text{ --- } 90°_x{}^{A,B}$$

As each rotation creates two components, the number of terms will increase exponentially with the number of steps. Fortuneally, 90° pulses retain only the sine component.

Initial 90° pulse

$$I_z^A + I_z^B \xrightarrow{90°_x{}^{A,B}} -I_y^A - I_y^B$$

since the problem is symmetrical we will only regard what happens to spin A:

Chemical shift during t_1 | spin-spin coupling during t_1

$$-I_y^A \xrightarrow{\Omega^A t_1} I_y^A \cos(\Omega^A t_1) \xrightarrow{\pi J_{AB} t_1} -I_y^A \cos(\Omega^A t_1)\cos(\pi J_{AB} t_1) + I_x^A I_z^B \cos(\Omega^A t_1)\sin(\pi J_{AB} t_1)$$

$$+ I_x^A \sin(\Omega^A t_1) \qquad + I_x^A \sin(\Omega^A t_1)\cos(\pi J_{AB} t_1) + I_y^A I_z^B \sin(\Omega^A t_1)\sin(\pi J_{AB} t_1)$$

second 90° pulse along x:

$90°_x{}^{A,B}$ ⟶

$-I_z^A \cos(\Omega^A t_1)\cos(\pi J_{AB} t_1)$	(I)	z magnetization of spin A gives no signal (Used in NOESY)
$- I_x^A I_y^B \cos(\Omega^A t_1)\sin(\pi J_{AB} t_1)$	(II)	DQ coherence of spins A/B not observable (Used in DQF-COSY)
$I_x^A \sin(\Omega^A t_1)\cos(\pi J_{AB} t_1)$	(III)	x magnetization of spin A => diagonal peak
$+ I_z^A I_y^B \sin(\Omega^A t_1)\sin(\pi J_{AB} t_1)$	(IV)	antiphase magnetization of spin B: will refocus to x magnetization of B during acquisition => cross peak

Evolution during acquisition (t_2): regard only terms III and IV, and keep only in phase x,y magnetization terms which are created after evolution of coupling:

$$\text{III} \xrightarrow{\Omega^A t_2,\ \pi J_{AB} t_2} I_x^A \sin(\Omega^A t_1)\cos(\pi J_{AB} t_1)\cos(\Omega^A t_2)\cos(\pi J_{AB} t_2) + I_y^A \sin(\Omega^A t_1)\cos(\pi J_{AB} t_1)\sin(\Omega^A t_2)\cos(\pi J_{AB} t_2) \quad \text{diagonal peak}$$

$$\text{IV} \xrightarrow{\Omega^B t_2,\ \pi J_{AB} t_2} -I_x^B \sin(\Omega^A t_1)\sin(\pi J_{AB} t_1)\cos(\Omega^B t_2)\sin(\pi J_{AB} t_2) - I_y^B \sin(\Omega^A t_1)\sin(\pi J_{AB} t_1)\sin(\Omega^B t_2)\sin(\pi J_{AB} t_2) \quad \text{cross peak}$$

- Always two sets of signals occur: Diagonal peaks (same Ω during t_1 and t_2) and cross peaks (Ω^A during t_1 and Ω^B during t_2 or vice versa).
- diagonal peak in phase doublet ($\cos(\pi J_{AB} t)$ in both $f_1$and f_2, cross peak anti phase with respect to J_{AB} in both f_1 and f_2
- cross and diagonal peaks 90° out of phase in both f_1 and f_2: III is along x and IV is along y axis at beginning of acquisition.

To avoid problems of dispersion peaks along the diagonal, the basic COSY spectrum is typically displayed in magnitude mode. That results in a loss in resolution and prevents accurate coupling constants to be measured.

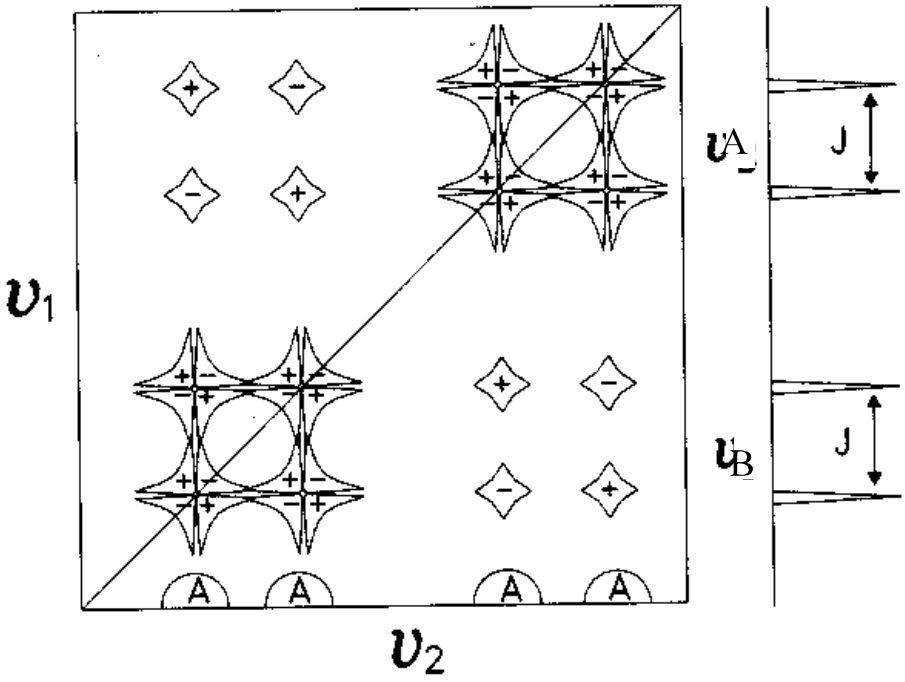
7.3. Double Quantum filtered COSY

Adding a third 90° pulse to the COSY experiment allows the double quantum term (II) to be converted into antiphase magnetization, which will evolve obsevable magnetization during acquisition:

$$- I_x^A I_y^B \xrightarrow{90°_x} -I_z^A I^B_y$$

Application of a four step phase cycle allows one to select only signal derived from this DQ term, and will result in diagonal and cross peaks both in anti phase and equal phase:

$(90°)_{x,y,-x,-y} - t_1 - (90°)_{x,y,-x,-y}\ (90°)_x$ acqusition$_{x,-x,x,-x}$ (+,-,+,-)



Schematic COSY spectrum. If the cross peaks are phased into absorption, the diagonal will appear 90° out of phase as dispersion peaks.

Thus a phase sensitive spectrum can be acquired in which both the diagonal and cross peaks can be phased. In addition, all singlet peaks will be suppressed as they will not evolve any DQ terms.

7.3.1. Appearance of DQF spectra:

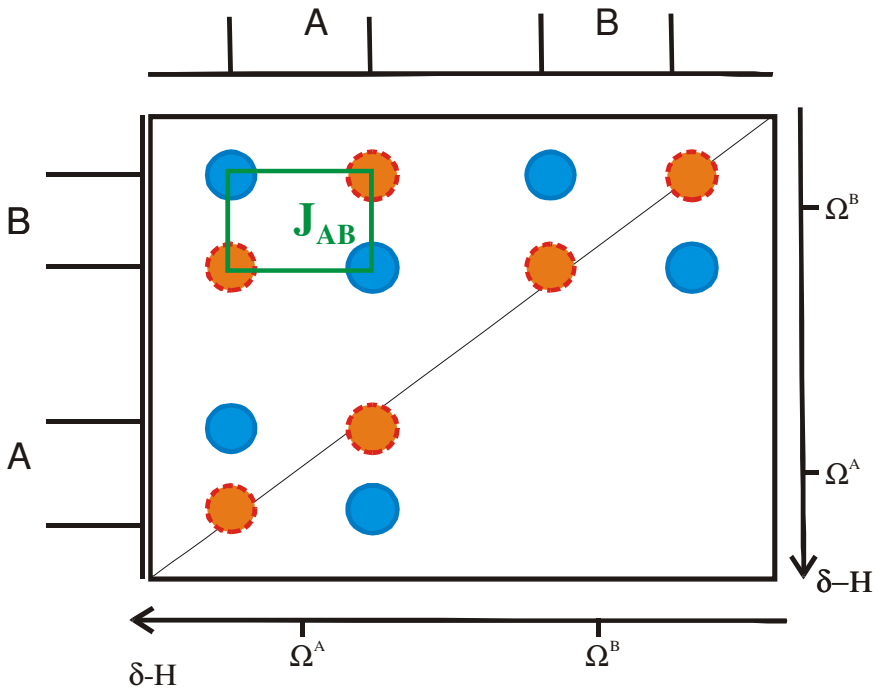
Two spin system: The cross peak will consist of four lines which appear anti phase in each dimension

Three spin system:

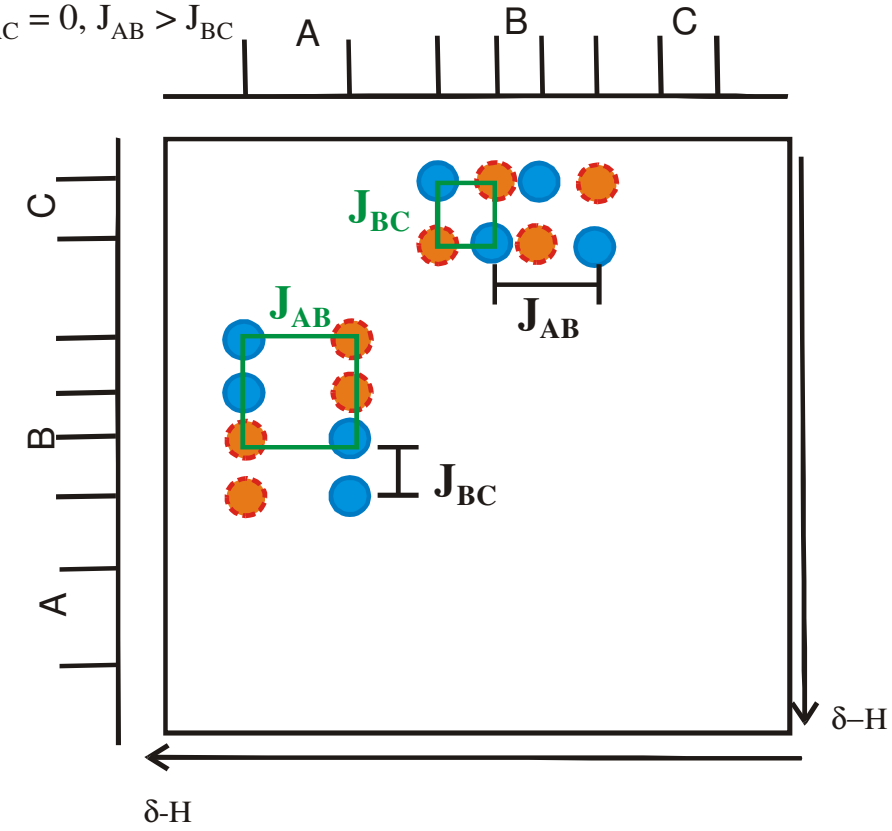
Now two types of coupling have to be considered: The coupling between the two spins comprising the cross peak is called the ***active*** coupling. All other couplings are referred to as ***passive*** couplings (they give additional splitting of the cross peak).

- active couplings give an anti phase splitting
- passive couplings cause in phase splitting
- Note that active and passive coupling are different for each cross peak.
- Up to 16 lines can occur for a multiplet.

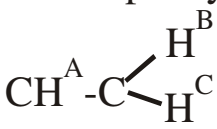
2 spin system: CH^{A}-CH^{B}



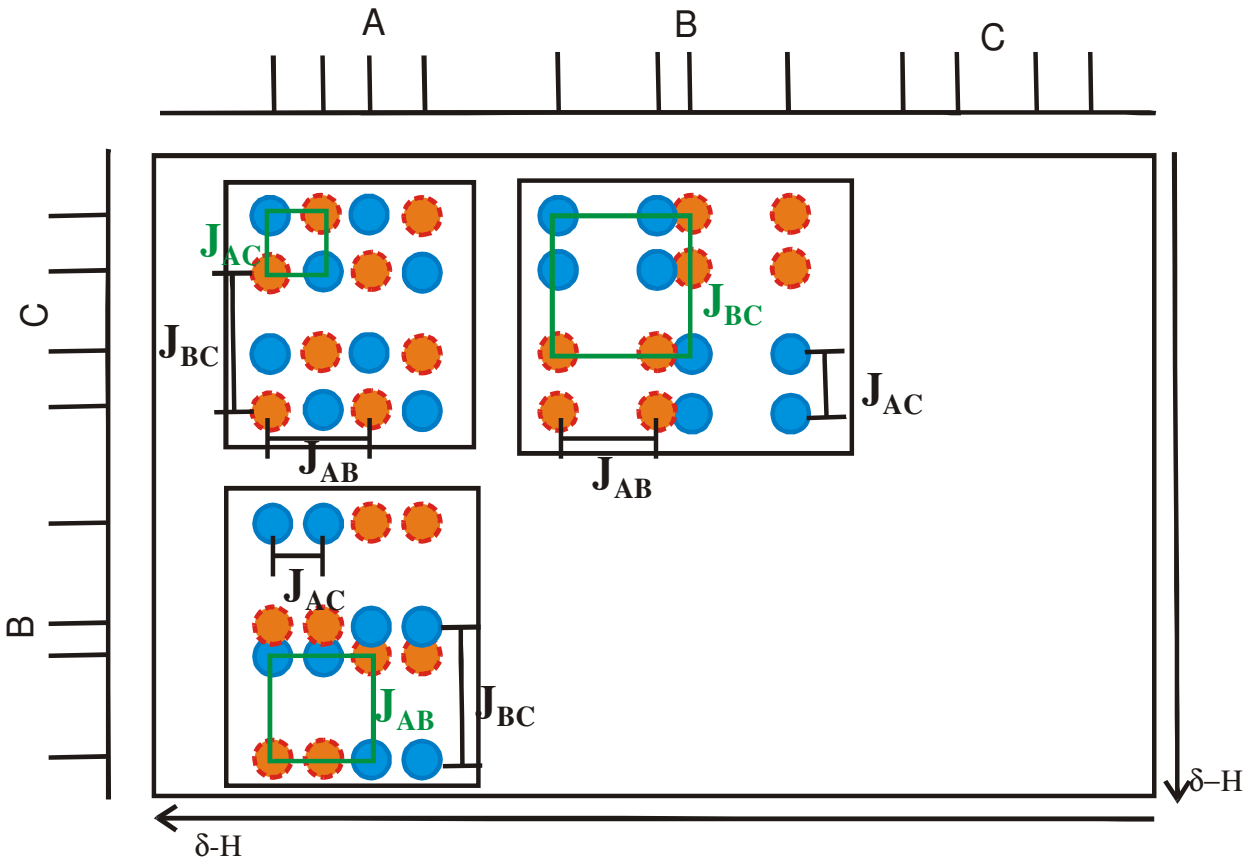
linear three spin system: CH^{A}-CH^{B}-CH^{C}
$J_{AC} = 0$, $J_{AB} > J_{BC}$



three spin system:

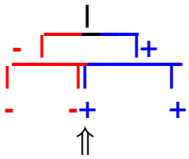


$J_{BC} > J_{AB} > J_{AC}$

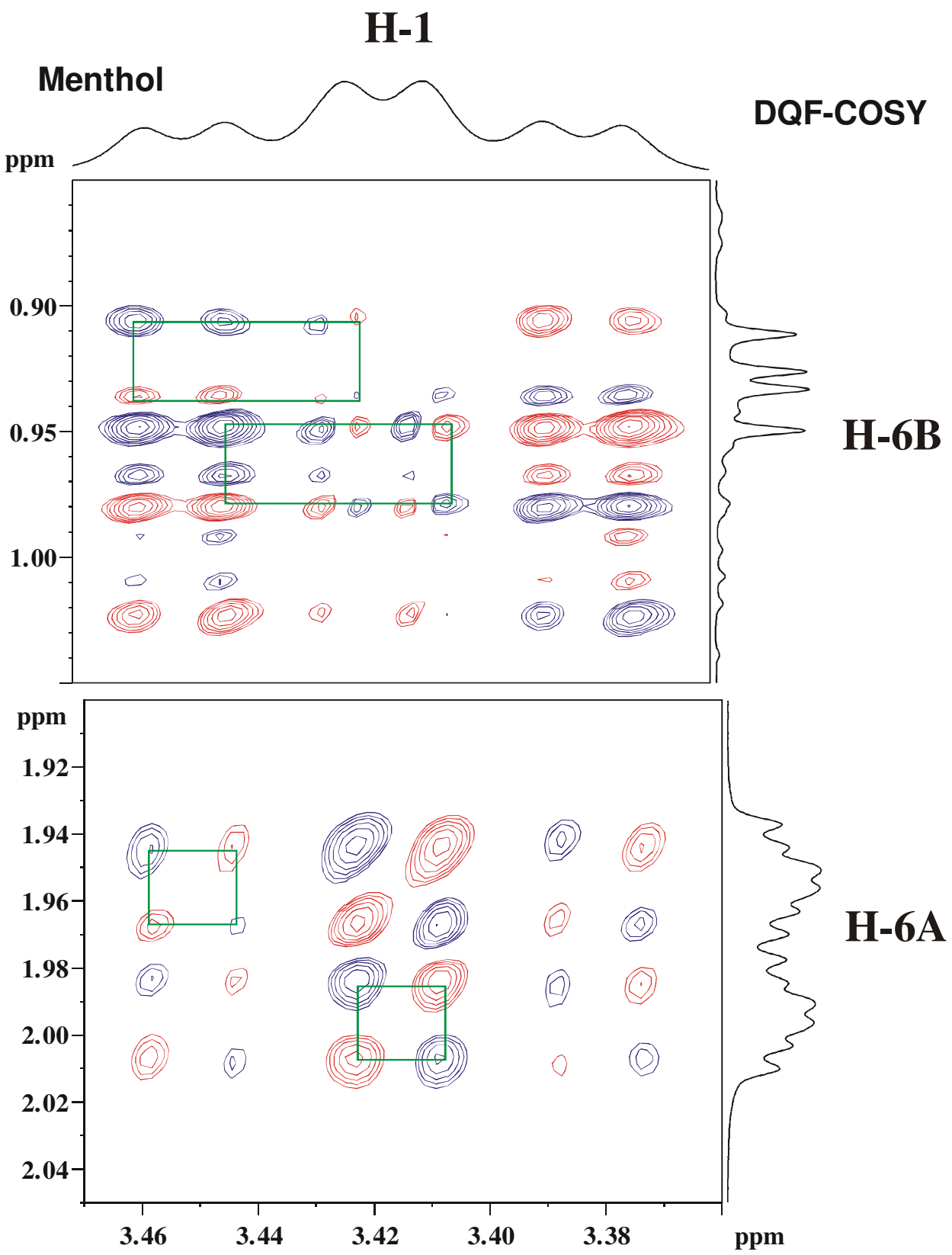


Schematic DQF-COSY spectra of two- and three spin systems. Active couplings are depicted in green, passive couplings is black. Note that the linear three spin system is just a special case of the three spin system with $J_{AC} = 0$.

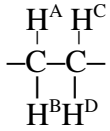
Consider the case when two couplings to chemical non equivalent partners become very similar, and one occurs as active and one as passive coupling. In that case positive and negative lines can overlap and partially or completely cancel (A/B and BC cross peaks in above example).



Cancellation


H-1
Menthol
DQF-COSY
ppm
0.90
0.95
1.00
H-6B
ppm
1.92
1.94
1.96
1.98
2.00
2.02
2.04
H-6A
3.46
3.44
3.42
3.40
3.38
ppm

Four coupled spins:



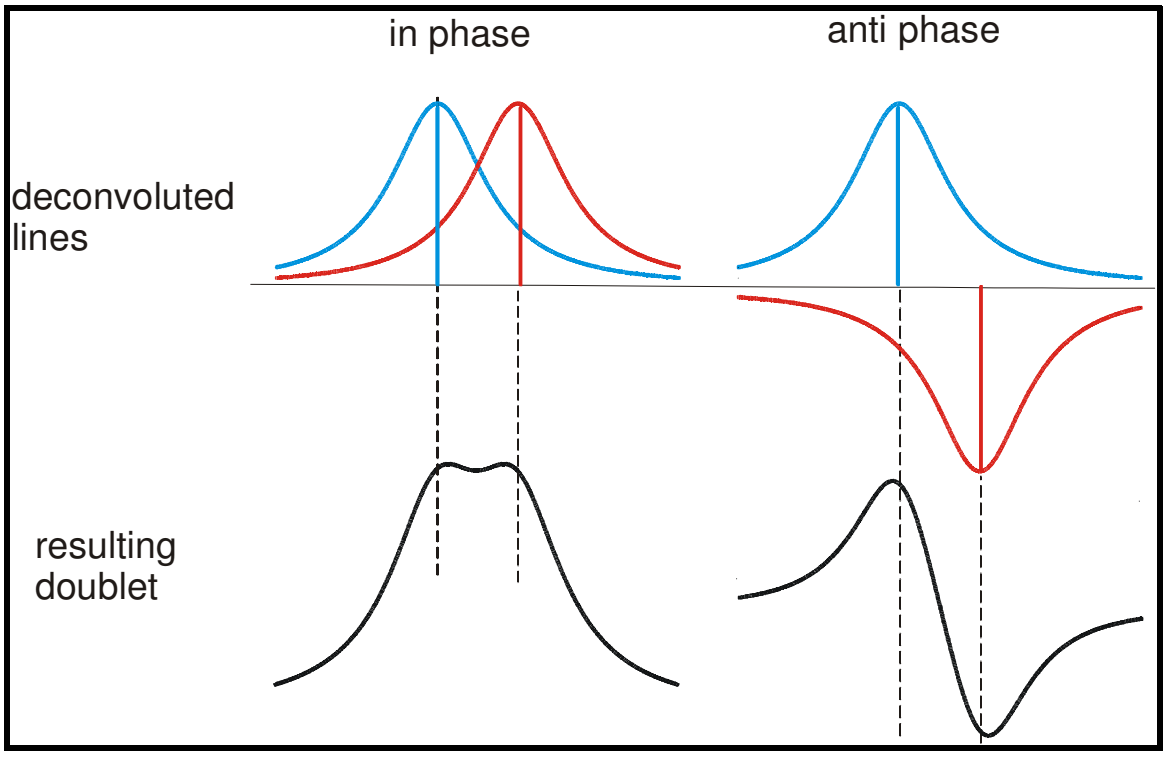
Up to$(2\cdot N\cdot I+1)^2 = 64$ lines can be observed (6 different J couplings).

Longer chains may have even more couplings, even thought typically some of the additional couplings will be close or equal to zero (more than three bonds). So the DQF-COSY patterns can become very complex and overlap and cancellation of lines will occur, making the analysis often very difficult or impossible.

Simplification of multiplet patterns is thus often a necessity. It can be obtained by obtaining enhanced COSY (E-COSY) spectra.

7.3.3. Small couplings and accuracy:

When the coupling constant becomes comparable to the line width (small coupling or broad lines) measurement of coupling constants will become less accurate. In particular, for in phase doublets (1D spectra or passive coupling in COSY) the apparent separation of the lines will be smaller than



the real coupling (or not visible at all), while for anti phase doublets (active coupling in COSY) the line separation will be larger than the true coupling.

Thus a method which would separate the individual multiplet lines would improve accuracy of coupling constant measurements. Again this will be possible to some extent by using the enhanced COSY method.

7.3.4. Experimental considerations

The choice of experiment (regular COSY vs. DQF COSY) will depend on the information required. If only general connectivity information is required the regular COSY will most of the times suffice as the DQF-COSY (or P.E. COSY, see below) will require more time to acquire.

Regular COSY:

- Optimized for low resolution as no fine structure of cross peaks needs to be resolved
- td[f1] = 64 - 128, can be performed in as little as 5-10 min for concentrated samples
- magnitude display, no need for phase correction
- gives basic H-H connectivity information only

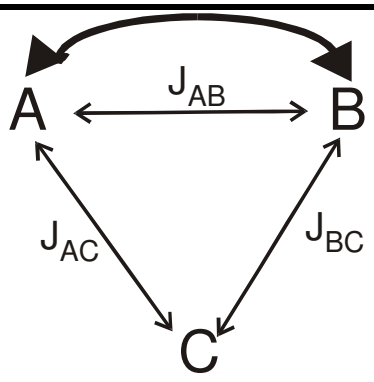
DQF-COSY (or P.E. COSY):

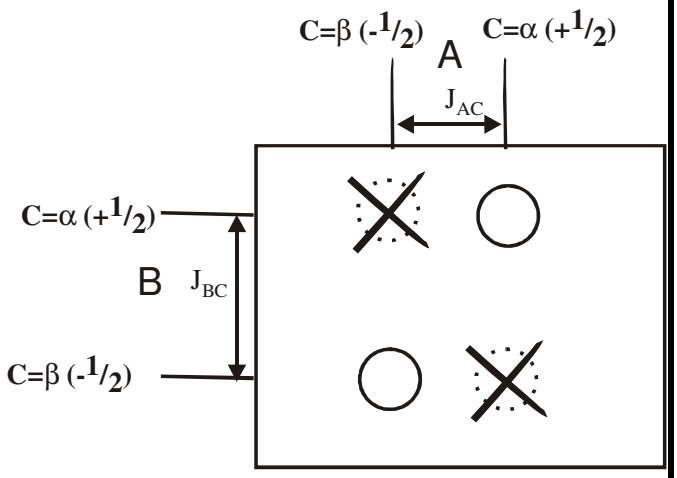
- Designed to resolve multiplet fine structure of cross peaks.
- td[f1] typically = 512 or larger. Takes one to several hours to run.
- Phase sensitive and will therefore require manual phase correction for useful results
- Should only be attempted when coupling constant information is to be extracted from 2D spectrum. EXCEPTION: Need for suppression of strong singlet peaks (H_2O samples) or cross peaks close to diagonal

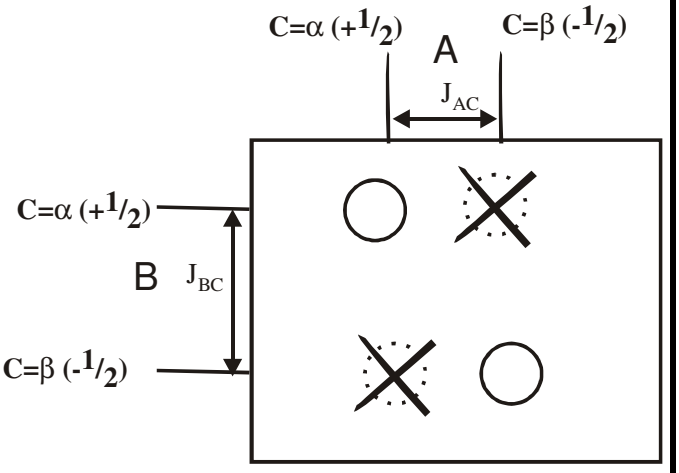
7.4. Enhanced COSY (E-COSY)

7.4.1 General Principle

Consider a system of three spins A,B,C coupled to each other by J_{AB}, J_{AC} and J_{BC}. In general any experiment correlating spins A and B without exciting the ***common coupling partner*** C will only result in peaks connecting multiplet lines with C in the same spin state, as no transitions from I_α^C to I_β^C (or vice versa) take place between t_1 and t_2.







General E-COSY principle for three spins. The active coupling is decoupled in both dimension.
TOP: J_{AC} and J_{BC} both >0 (equal sign)
BOTTOM: J_{AC} <0, J_{BC} > 0 (opposite sign).

The splitting by the passive coupling to the common partner C can be obtained without overlap of the doublet components.

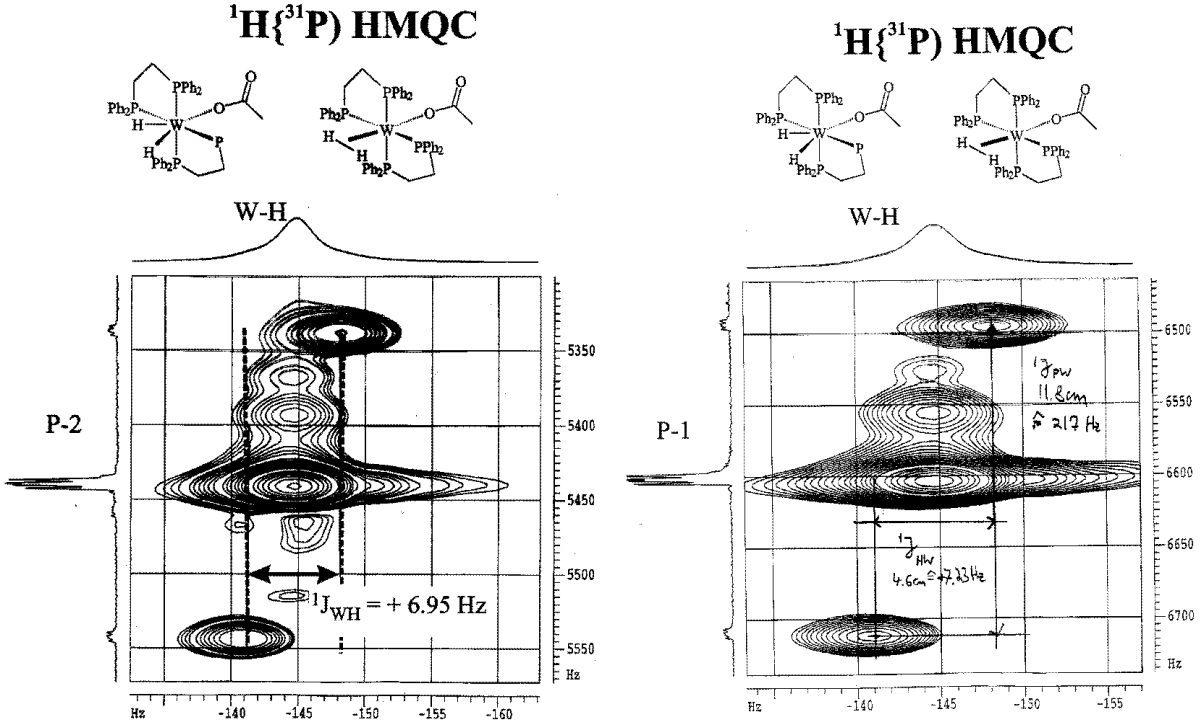
Different relative signs of the two couplings give different spectra and can thus be used to measure relative sign of coupling constants.

Out of the four peaks resulting from two doublets in the DQF-COSY only two are observed in the case of an E. COSY multiplet resulting in a separation of the individual doublet lines. The coupling thus can be measured without overlap even in the case of very small couplings as long the other passive coupling is large enough.

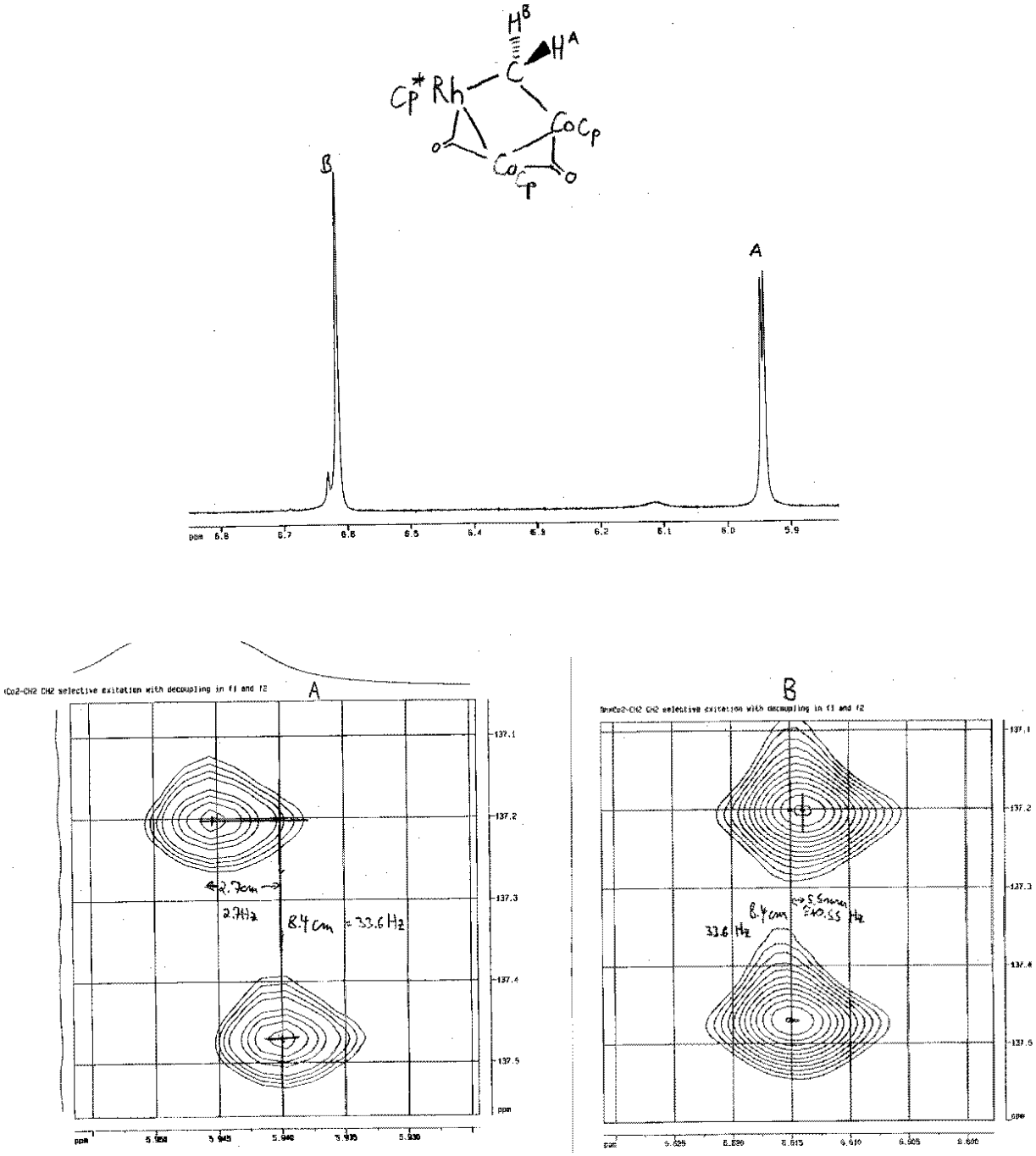
Furthermore the shape of the multiplet depends on the relative signs of the two passive couplings constants which therefore can be experimentally determined with such experiments.

7.4.2. E. COSY in HSQC and HMQC spectra

If A,B and C are all different nucleotides a correlation of A and B via HSQC or HMQC will show E. COSY type peaks from coupling to C.



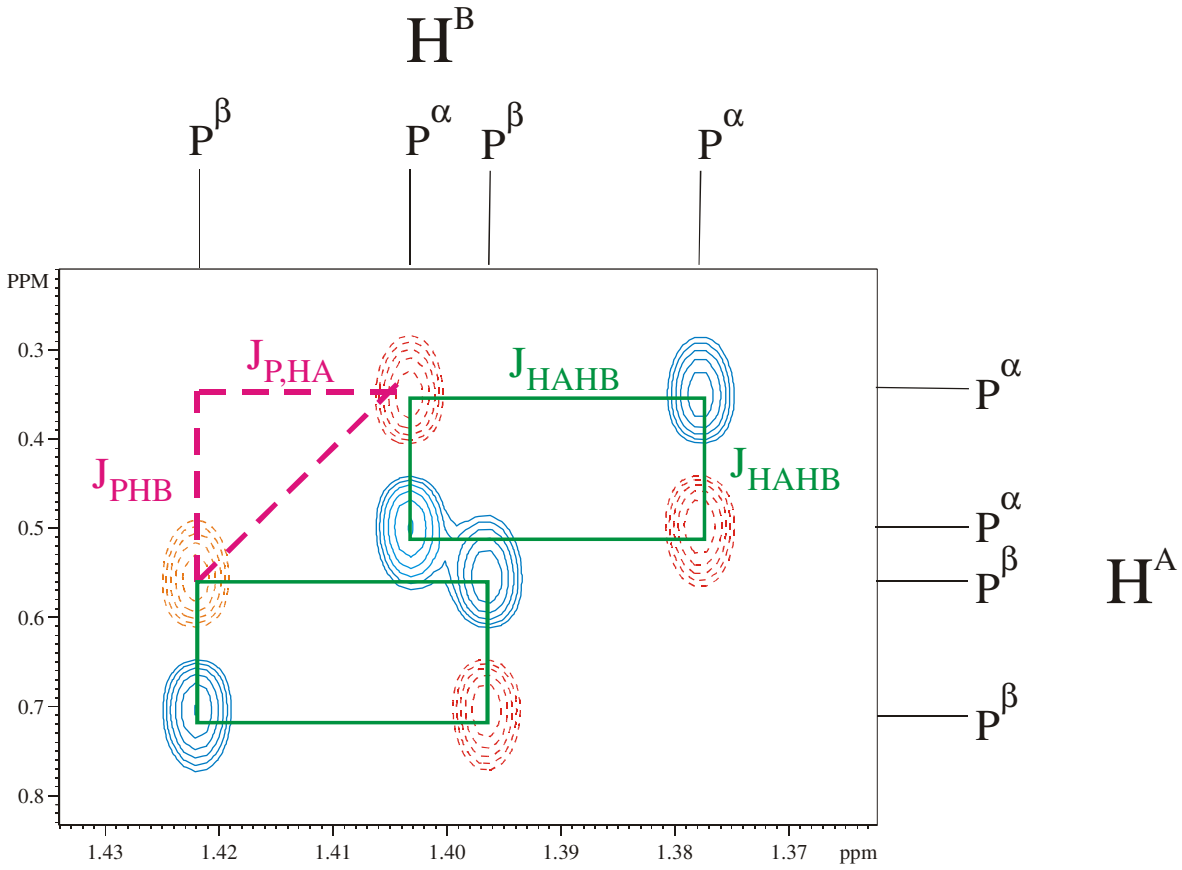
$^1H/^{31}P$ HMQC spectra of $H_2W(\eta^2\text{-}PC_2H_4P)_2Ac$. The satellites from the coupling of ^1H to ^{183}W (abundance 14%) are not resolved in the 1D proton spectrum. However the coupling is clearly visible in the 2D $^1H/^{31}P$ spectrum due to the large one bond coupling $^1J_{31P,183W}$ which separates the two douplet components not only from each other but also from the large main singlet (^1H bound to I = 0 ^{182}W, ^{184}W and ^{186}W). One can also see that $^1J_{P,W}$ and $^1J_{H,W}$ have the same sign (both positive as expected for one bond coupling between I = + ½ nuclei).



$^{1}H\{^{13}C\}$ HSQC spectrum of $Cp^{*}Rh(CpCo)_2(\mu_2\text{-}CO)_2$. The large passive ^{13}C-^{103}Rh coupling allows the small ^{1}H-^{103}Rh coupling to be observed even when it is not resolved in the 1D ^{1}H spectrum (H^B). One can see that $^{2}J_{HB,Rh}$ has the same sign as $^{1}J_{C,Rh}$ whereas $^{2}J_{HA,Rh}$ has the opposite sign. If one assumes $^{1}J_{C,Rh} > 0$, then $^{2}J_{HA,Rh} < 0$ and $^{2}J_{HB,Rh} > 0$.

7.4.3. E. COSY in DQF or regular COSY spectra

If A and B are of the same isotope (usually ^1H) and C is a hetero nucleus the cross peaks in $^1H/^1H$ COSY spectra will be split in an E. COSY type fashion by the passive couplings A-C and B-C. In the example (simulated spectrum of $Ph_2P=CH^A-CH^BR_2$)the passive coupling is to a ^{31}P nucleus:



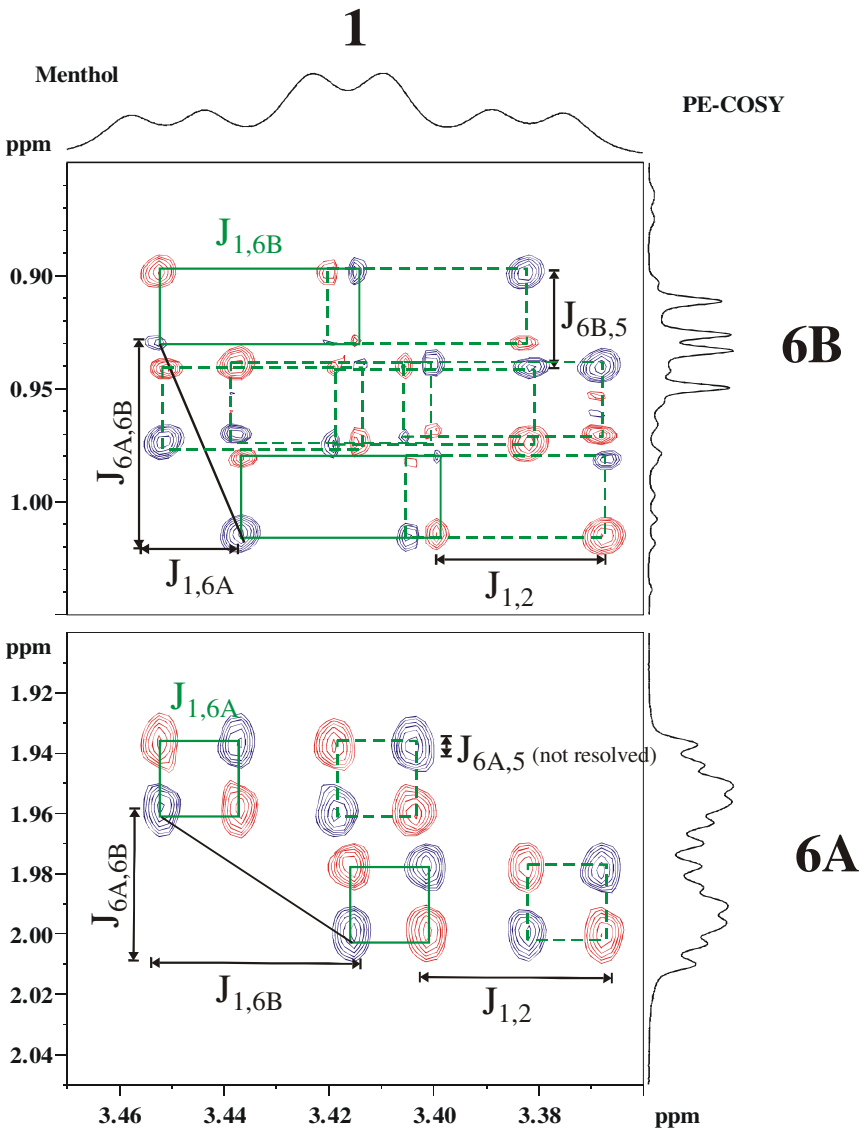
7.4.4. Homonuclear spin systems and P.E. COSY

An E. COSY type pattern in $^1H/^1H$ COSY would simplify the patterns observed in DQF-COSY spectra. However, in homonuclear spin systems the condition that the passive coupling partner is not to be exited during the experiment can not be fulfilled as all pulses will be applied to all nuclei. However, it can be shown if the second 90° pulse in the COSY experiment is replaced by a pulse smaller than 90° (the best value is 36°) than correlations between lines with the passive coupling partner in different spin states are much weaker than the ones between equal spin states:

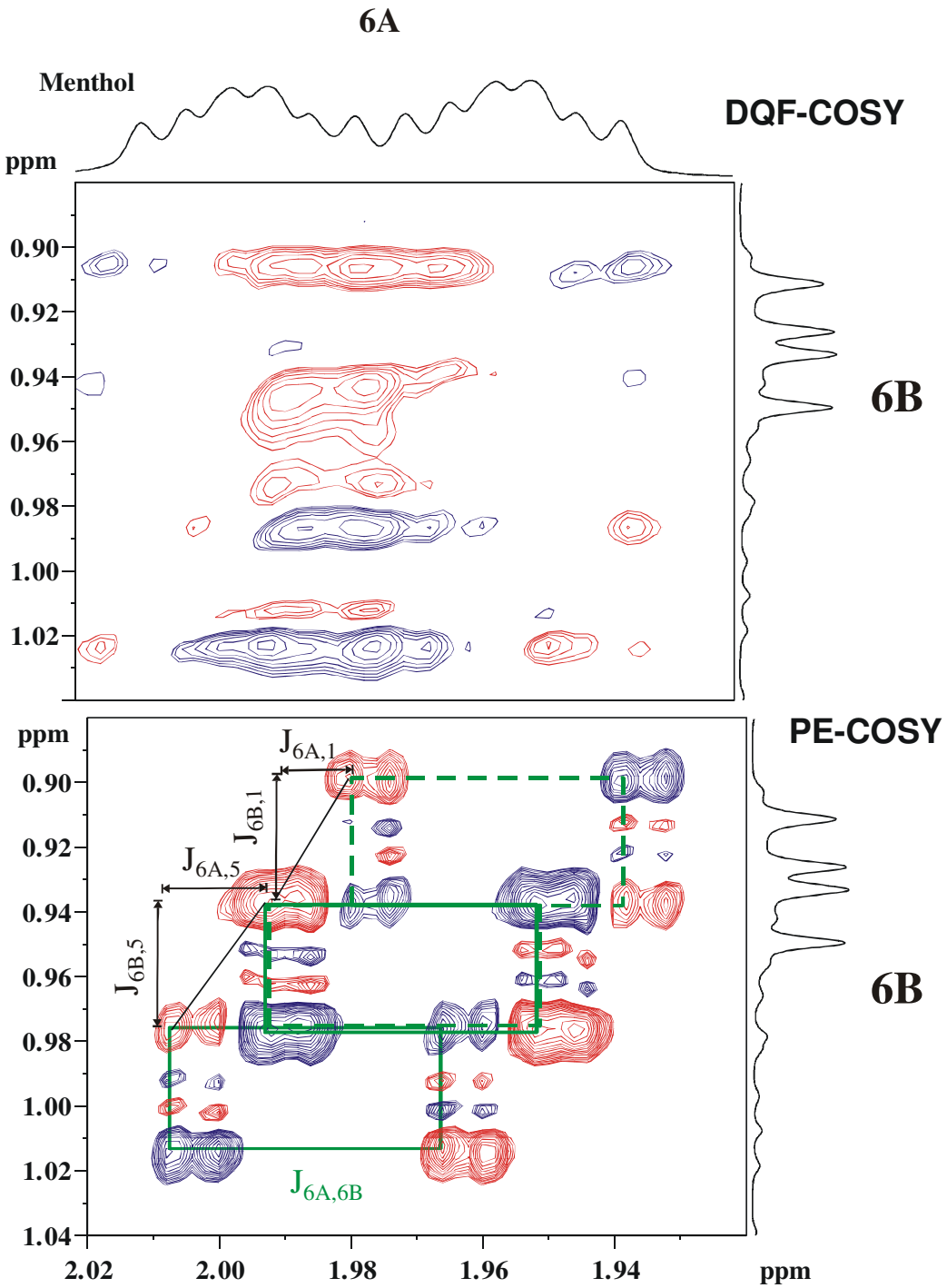
In order to solve the problem of the out of phase diagonal encountered in the two pulse COSY experiment a phase cycle is employed to subtract the diagonal:

$(90°)_{x,x}$ — t_1 — $(18°)_{x,x}$ $(18°)_{x,-x}$ acquisition$_{x,-x}$(add, subtract)

By splitting the second pulse in two one performs one scan with 18+18 = 36° (cross and diagonal) and subtracts the spectrum with 18-18 = 0° (diagonal only). That results in a spectrum with a reduced diagonal which can be acquired in a phase sensitive fashion and which will exhibit E-COSY type multiplet patters. This experiment is called P.E. COSY for ***P***rimitive ***E***nhanced COSY (implying that there is a better but also more complicated way to achieve such a spectrum).



P.E. COSY spectrum of the 1/6 cross peaks of menthol. Note that only those passive couplings involving partners common to the active coupling partners (1,6B/6A/6B and 1,6A/6A/6B) result in an E-COSY type pattern.



Comparison of the DQF and P.E-COSY spectra of the H6A/H6B cross peak in menthol. Only the P.E. COSY allows a useful analysis of the pattern. Note that H^{6A} shows a long range coupling ($^4J_{H6A,H4?}$?) not resolved for H^{6B}.