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Multiple Quantum Filters for Elucidating NMR Coupling Networks

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The elucidation of molecular structure by NMR spectroscopy relies upon the establishment of connectivities between nuclear spins through scalar J couplings. a convenient technique for tracing out coupling networks is two-dimensional (2-D) correlation spectroscopy.[1-5] The experiment is simple and informative. The response to a pair of 90° pulses separated by a variable delay t_1 (evolution time) is measured and Fourier transformed in two dimensions. The resulting 2-D spectrum exhibits diagonal peaks representing the inequivalent nuclear sites and cross-peaks for J couplings between sites.

In this communication, we describe multiple quantum filtering to further enhance 2-D correlation spectroscopy. By selecting coherence transfer between evolution and detection periods proceeding through a certain order of multiple quantum coherence (MQC), it is possible to purge spectra from undesired features and to focus on relevant peaks. Double quantum selection has been used before for the retrieval of doubly labeled molecules from natural abundance ^{13}C resonance,[6] for selection of two-proton spin systems,[7] and for selective removal of magnetization.[8]

Multiple quantum filtering can be achieved by the sequence $90°(\varphi)$–t_1–$90°(\varphi + \psi)$–$90°(\psi)$-acquisition. For a p-quantum filter, the phase φ is cycled through the values $\varphi = k\pi/p$, $k = 0, 1, 2, ..., 2p - 1$. To ensure quadrature detection in ω_1, the phase cycle is performed for $\psi = 0$ and for $\psi = \pi/2$. The resulting signals are alternately added and subtracted.[9] By the third 90° pulse, multiple quantum coherence, generated by the second pulse, is converted back into observable magnetization. We should note that a multiple quantum filter of order p is also transparent for odd multiple orders $p(2m + 1)$, $m = 0, 1, 2....$ This is, however, without consequence for the simplification of spectra.

In the following, we describe possible applications of multiple quantum filtering:

Suppression of Singlets. Singlets, such as peaks of many common solvents, cannot produce MQC and are eliminated by multiple quantum filters. Figure 1a presents a 2-D correlation spectrum of 1,3-dibromobutane, $CH_2BrCH_2CHBrCH_3$ (I) with strong solvent peaks from Me_2SO (2.5 ppm) and dioxane (3.5 ppm). A comparable spectrum from use of a double quantum filter is shown in Figure 1b. The solvent peaks have been suppressed without significantly affecting cross-peaks.

Reduction of Dominant Diagonal Peaks. Cross-peak multiplet lines have alternating signs and tend to cancel when incompletely resolved. Diagonal peak multiplets, however, are of equal phase and remain for complex spectra as dominant ridges.[3,4,10] The transfer through MQC makes diagonal peak multiplets of alternating sign such that incomplete resolution reduces them to the same extent as cross-peak multiplets.

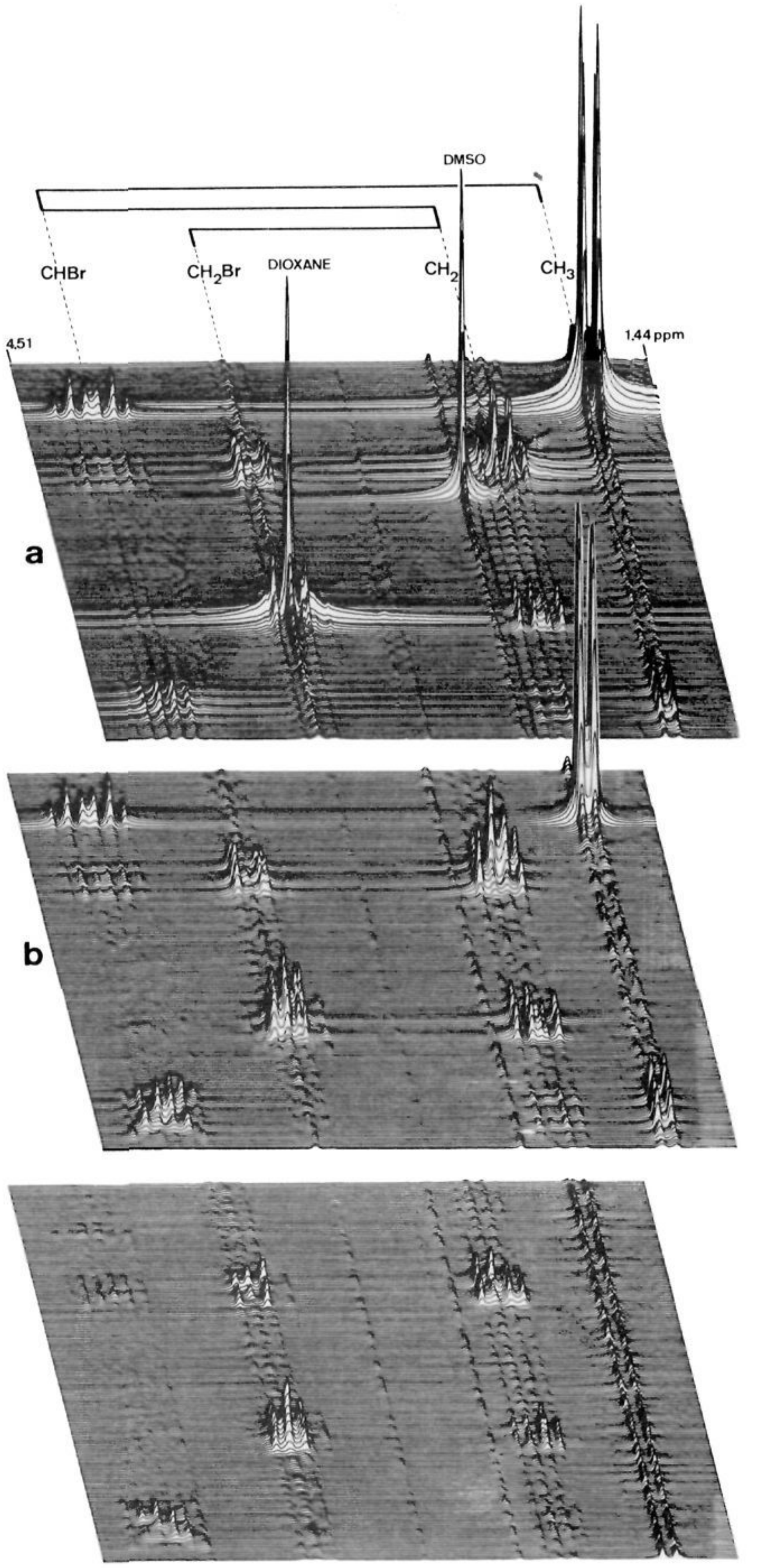

Figure 1. 2-D correlated 90-MHz proton spectra of 1,3-dibromobutane in absolute value representation: (a) conventional two-pulse experiment (4 scans); (b) same as a with double quantum filter (16 scans); (c) same as a with triple quantum filter (24 scans). FID's for 256 t_1 values and with 512 t_2 samples are recorded and supplemented in both dimensions by an equal number of zeros. On top, the linear coupling network is indicated.

Selection or Suppression of Specific Coupling Patterns. The appearance or absence of peaks in a 2-D correlation spectrum with multiple quantum filtering is governed by the following selection rules: (i) The appearance of a *diagonal peak* in a p-quantum-filtered spectrum implies that the spin in question has resolved couplings to p-1 equivalent or nonequivalent spins. (ii) The appearance of a *cross-peak* between two spins in a p-quantum-filtered spectrum indicates that, in addition to their direct coupling, there are nonvanishing couplings to a common set of at least p-2 additional spins. These rules hold strictly for weak coupling and are discussed in ref 11.

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Figure 1c shows a 2-D correlated spectrum of I with use of a triple quantum filter. In agreement with expectations, the methyl peak is absent as there is only one resolved coupling to CHBr. In the weak coupling approximation of a linear $A_2M_2RX_3$ coupling network, no cross-peaks should appear at all for triple or higher quantum filtering. However, the weak chemical nonequivalence of the CH_2 groups and the violation of the weak coupling condition ($\delta/J \simeq 16$) allow the appearance of cross-peaks between the two CH_2 groups. Due to the restriction of coherence transfer through certain orders of multiple quantum coherence, the sensitivity is somewhat reduced. For example, a double quantum filter reduces the cross-peak amplitudes by a factor 2 (compare Figure 1a and b with a total of 4 and 16 scans, respectively).

Higher order multiple quantum filters gradually decrease the complexity of 2-D spectra and focus attention on spin systems with intricate coupling networks. This feature can also be utilized to simplify 1-D proton spectra by inserting a multiple quantum filter in the excitation sequence, for example in the form: $90°(\varphi)-\tau-180°(\varphi)-\tau-90°(\varphi + \psi)-90°$-acquisition ($\psi = 0$ for p even and $\psi = \pi/2$ for p odd). In this way, transitions of spin subsystems with accessible multiple quantum transition of order p are excited exclusively. For example, a four-quantum filter eliminates, in addition to all one-, two-, and three-spin systems, all linear coupling networks of the type ··A-B-C-D···.[11] Multiple quantum filters have the potential to facilitate the analysis of complex spin systems while retaining the accustomed data presentation form of standard 2-D and 1-D NMR spectroscopy.

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The Mechanism of Sodium Borohydride–Cobaltous Chloride Reductions

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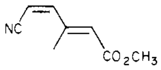
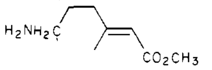
The combination of sodium borohydride with cobalt(II),[1] nickel(II),[1,2] copper(II),[3] and rhodium(III)[4] halides has been employed to reduce functional groups such as nitriles, amides, and olefins,[3,5] which are inert to $NaBH_4$ alone. Despite frequent use,[6–15] the nature of the actual reducing species in these complex mixtures remains obscure. For example, the reaction of $NaBH_4$ with $CoCl_2$ in CH_3OH is exothermic and instantly deposits a black granular precipitate of cobalt boride (Co_2B)[16–18] while steadily evolving hydrogen. Conceivable reducing agents in such a mixture, to name only a few, include (a) the heterogeneous Co_2B/H_2 system, which is known to hydrogenate olefins and nitriles,[19] (b) homogeneous cobalt hydrogenation catalysts,[20] or (c) soluble cobalt borohydride complexes,[17–21] some of which constitute good hydride donors. Herein we report experiments that rule out the above mentioned possibilities and strongly suggest that cobalt boride, by coordinating to certain functional groups, catalyzes their heterogeneous reduction by $NaBH_4$. This understanding has led to the rational design of a superior reagent, $Co_2B/t\text{-}BuNH_2{\cdot}BH_3$, for more efficient, selective reduction of nitriles.

Table I. Catalytic $Co_2B/NaBH_4$ Reductions

substrate	conditions[a]	product (yield, %)
PhCN	A, B; rt, 4 h	$PhCH_2NH_2$ (79–85)
$PhCH_2CN$	A, rt, 2 h	$PhCH_2CH_2NH_2$ (74)
 1	A, 0 °C, 8 h[b]	 2 (60)[c]
$PhCONH_2$	A, reflux, 36 h	$PhCH_2NH_2$ (8) (see ref 23)
$PhCH{=}CHCO_2CH_3$	B, rt, 2 h	$PhCH_2CH_2CO_2CH_3$ (85)
$CH_3(CH_2)_5C{\equiv}CH$	A, rt, 3 h	octane (83)

[a] Conditions: A, Co_2B (1 equiv) + $NaBH_4$ (5–10 equiv) in CH_3OH; B, Co_2B (0.1 equiv) + $NaBH_4$ (5 equiv) in CH_3OH; rt = room temperature. [b] Ethylenediamine (5 equiv) was added to this reaction mixture. [c] $NaBH_4$ alone reduced the double bond but not the nitrile.

When $CoCl_2$ was treated with 5 mol equiv of $NaBH_4$ in CH_3OH for 10 min, 95% of the cobalt was deposited as Co_2B, an air-stable solid that could be isolated by filtration.[22] Two experiments demonstrated that the residual dissolved cobalt was most likely a Co(II) species. Adding more $NaBH_4$ precipitated further traces of Co_2B; moreover, supernatant acidified with HCl turned the faint blue characteristic of $CoCl_2$. A weighed sample was reexposed to $NaBH_4/CH_3OH$ with negligible catalyst decomposition to show that the boride was stable to the reduction conditions; again, only traces of leached soluble cobalt(II) salts were detected.

Fresh supernatant from a $CoCl_2/NaBH_4$ reaction was by itself incapable of reducing benzonitrile. The boride alone, although known to occlude some H_2 during its formation,[16] was also ruled out as the reducing agent. However, when equimolar quantities of benzonitrile and Co_2B were mixed, we unexpectedly found most of the nitrile to be strongly adsorbed on the solid surface; it could be released by ammonolysis (28% NH_4OH) or by dissolving the boride in aqueous HCl. Control hydrolyses further demonstrated that Co_2B bound to benzonitrile easily survived acidic conditions that otherwise decomposed the pure boride, or boride containing benzylamine. This protective effect exerted by nitriles has not been noted before.[23]

When Co_2B (0.2 equiv) in CH_3OH was stirred under 1 atm of H_2 with either benzonitrile or benzamide, no benzylamine was observed, even after 11 days. Altogether these experiments strongly suggested that neither adsorbed H_2, exogenous H_2, nor soluble cobalt-containing boron hydride species played any sig-

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(22) Caution: Co_2B becomes pyrophoric when dried under vacuum (6 h). It can be air-dried but is most safely stored moist with solvent.

(23) In contrast, benzamide was not adsorbed on Co_2B to any appreciable extent, and we were unable to reproduce its reported reduction to benzylamine by using $NaBH_4/CoCl_2$.[1] Others[13] have apparently had similar difficulties with primary amides.