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Analytical Polarization Transfer Functions for Four Coupled Spins $\frac{1}{2}$ under Isotropic Mixing Conditions

Burkhard Luy, Oliver Schedletzky, and Steffen J. Glaser[1]

Institut für Organische Chemie, J. W. Goethe-Universität, Marie-Curie-Strasse 11, D-60439 Frankfurt, Germany

Analytical polarization transfer functions are presented for spin systems consisting of four spins $\frac{1}{2}$ with arbitrary coupling constants under isotropic mixing conditions. In addition, simplified transfer functions were derived for symmetric coupling topologies. Based on these transfer functions optimal durations for the mixing period can be determined for correlations of interest. © 1999 Academic Press

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INTRODUCTION

Isotropic mixing (*1, 2*) has become one of the most important techniques for the transfer of polarization in high-resolution NMR spectroscopy. Many homonuclear and heteronuclear experiments use isotropic mixing steps to maximize polarization transfer. The efficiency of isotropic mixing experiments depends critically on the duration of the mixing time. A rational choice of the optimum mixing time can be made based on coherence or polarization transfer functions which describe the dynamics of the transfer of interest. Although transfer functions can be calculated numerically with the help of simulation programs (*3–9*), closed form analytical expressions for important transfer functions are highly desirable.

Analytical isotropic mixing transfer functions have been reported for a number of special cases. For a system consisting of two isotropically coupled spins $\frac{1}{2}$ the transfer functions were derived by Braunschweiler and Ernst (*1*). For the general case of three coupled spins $\frac{1}{2}$ the coherence and polarization transfer functions have recently been reported (*10*). Polarization and coherence transfer functions have also been reported for isotropically coupled A_2X_2 and A_2X_3 spin systems and for AX_N spin systems with $N \leq 6$ (*11, 12*). Furthermore it has been shown that the evolution frequencies in an A_MX_N system are always identical to the evolution frequencies in a corresponding AX_{M+N-1} system (*13*). Analytical polarization transfer functions for a linear spin chain and a star-like coupling topol-

ogy consisting of four spins with equal coupling constants were derived by Majumdar (*14*). In this article, analytical polarization transfer functions are presented for the general case of four coupled spins $\frac{1}{2}$ under isotropic mixing conditions with arbitrary coupling constants J_{ij}. Furthermore the special cases of an AMX_2-type and a linear AM_2X-type spin system are discussed in detail and it is shown that the A_2X_2-type and the AX_3-type spin systems can be reduced to the case of a four-spin system with identical coupling constants $J_{ij} = J$.

THEORY

For a spin system consisting of four coupled spins $\frac{1}{2}$, the ideal isotropic mixing Hamiltonian has the form

$$\mathcal{H}_{\text{iso}} = 2\pi \sum_{i<j}^{4} J_{ij} I_i I_j. \qquad [1]$$

In analogy to the case of three coupled spins under isotropic mixing conditions, polarization transfer functions can be determined if the eigenvalues and eigenfunctions of $\mathcal{H}_{\text{iso}}$ are known (*10*). As

$$[\mathcal{H}_{\text{iso}}, F^2] = 0 \qquad [2]$$

and

$$[\mathcal{H}_{\text{iso}}, F_z] = 0 \qquad [3]$$

a convenient basis is formed by a set of simultaneous eigenfunctions $|J, m\rangle$ of the square of the total spin operator F^2 and of F_z. These eigenfunctions may readily be constructed with the help of Clebsch–Gordan coefficients (*15*). Note that the eigenfunctions depend in general on the order in which the single-spin functions are combined. Here we combined spins 1, 2 and 3, 4 first, before the two pairs were combined (see Table 1).

[1] To whom correspondence should be addressed. Fax: +49 69 7982 9128. E-mail: sg@org.chemie.uni-frankfurt.de.

TABLE 1
Simultaneous Eigenfunctions of F^2 and F_z

$|2, 2\rangle = |\alpha\alpha\alpha\alpha\rangle$

$|2, 1\rangle = \frac{1}{2}(|\alpha\alpha\alpha\beta\rangle + |\alpha\alpha\beta\alpha\rangle + |\alpha\beta\alpha\alpha\rangle + |\beta\alpha\alpha\alpha\rangle)$

$|2, 0\rangle = \frac{1}{\sqrt{6}}(|\alpha\alpha\beta\beta\rangle + |\alpha\beta\alpha\beta\rangle + |\alpha\beta\beta\alpha\rangle + |\beta\alpha\alpha\beta\rangle$
$\qquad\qquad + |\beta\alpha\beta\alpha\rangle + |\beta\beta\alpha\alpha\rangle)$

$|2, -1\rangle = \frac{1}{2}(|\alpha\beta\beta\beta\rangle + |\beta\alpha\beta\beta\rangle + |\beta\beta\alpha\beta\rangle + |\beta\beta\beta\alpha\rangle)$

$|2, -2\rangle = |\beta\beta\beta\beta\rangle$

$|1, 1, 1\rangle = \frac{1}{2}(|\alpha\alpha\alpha\beta\rangle + |\alpha\alpha\beta\alpha\rangle - |\alpha\beta\alpha\alpha\rangle - |\beta\alpha\alpha\alpha\rangle)$

$|1, 0, 1\rangle = \frac{1}{\sqrt{2}}(|\alpha\alpha\beta\beta\rangle - |\beta\beta\alpha\alpha\rangle)$

$|1, -1, 1\rangle = \frac{1}{2}(|\alpha\beta\beta\beta\rangle + |\beta\alpha\beta\beta\rangle - |\beta\beta\alpha\beta\rangle - |\beta\beta\beta\alpha\rangle)$

$|1, 1, 2\rangle = \frac{1}{\sqrt{2}}(|\alpha\beta\alpha\alpha\rangle - |\beta\alpha\alpha\alpha\rangle)$

$|1, 0, 2\rangle = \frac{1}{2}(|\alpha\beta\alpha\beta\rangle + |\alpha\beta\beta\alpha\rangle - |\beta\alpha\alpha\beta\rangle - |\beta\alpha\beta\alpha\rangle)$

$|1, -1, 2\rangle = \frac{1}{\sqrt{2}}(|\alpha\beta\beta\beta\rangle - |\beta\alpha\beta\beta\rangle)$

$|1, 1, 3\rangle = \frac{1}{\sqrt{2}}(|\alpha\alpha\alpha\beta\rangle - |\alpha\alpha\beta\alpha\rangle)$

$|1, 0, 3\rangle = \frac{1}{2}(|\alpha\beta\alpha\beta\rangle - |\alpha\beta\beta\alpha\rangle + |\beta\alpha\alpha\beta\rangle - |\beta\alpha\beta\alpha\rangle)$

$|1, -1, 3\rangle = \frac{1}{\sqrt{2}}(|\beta\beta\alpha\beta\rangle - |\beta\beta\beta\alpha\rangle)$

$|0, 0, 1\rangle = \frac{1}{\sqrt{3}}(|\alpha\alpha\beta\beta\rangle + |\beta\beta\alpha\alpha\rangle) - \frac{1}{2\sqrt{3}}(|\alpha\beta\alpha\beta\rangle + |\alpha\beta\beta\alpha\rangle$
$\qquad\qquad + |\beta\alpha\alpha\beta\rangle + |\beta\alpha\beta\alpha\rangle)$

$|0, 0, 2\rangle = \frac{1}{2}(|\alpha\beta\alpha\beta\rangle - |\alpha\beta\beta\alpha\rangle - |\beta\alpha\alpha\beta\rangle + |\beta\alpha\beta\alpha\rangle)$

In the basis $|J, m\rangle$ the Hamiltonian is block diagonal with nine submatrices: five identical 1×1 matrices

$$\mathbf{A} = 2\pi(\Sigma + A) = \frac{\pi}{2} \sum_{i<j}^{4} J_{ij} = \lambda \qquad [4]$$

for $J = 2$ and $m = 2, 1, 0, -1, -2$; three identical 3×3 matrices

$$\mathbf{B} = 2\pi \begin{pmatrix} B_{11} & B_{12} & B_{13} \\ B_{21} & B_{22} & B_{23} \\ B_{31} & B_{32} & B_{33} \end{pmatrix}$$

$$= 2\pi \begin{pmatrix} (\Sigma - A) & \sqrt{2}C & \sqrt{2}B \\ \sqrt{2}C & (-2\Delta - \Sigma) & D \\ \sqrt{2}B & D & (2\Delta - \Sigma) \end{pmatrix} \qquad [5]$$

for $J = 1$ and $m = 1, 0, -1$; and one 2×2 matrix for $J = 0$

$$\mathbf{C} = 2\pi \begin{pmatrix} (\Sigma - 2A) & -\sqrt{3}D \\ -\sqrt{3}D & -3\Sigma \end{pmatrix} \qquad [6]$$

with

$$\Sigma = \frac{J_{12} + J_{34}}{4}; \qquad\qquad \Delta = \frac{J_{12} - J_{34}}{4}$$

$$A = \frac{J_{13} + J_{14} + J_{23} + J_{24}}{4}; \qquad B = \frac{J_{13} - J_{14} + J_{23} - J_{24}}{4}$$

$$C = \frac{-J_{13} - J_{14} + J_{23} + J_{24}}{4}; \qquad D = \frac{J_{13} - J_{14} - J_{23} + J_{24}}{4}.$$
$$[7]$$

The eigenvalue λ of matrix $\mathbf{A}$ is given by Eq. [4]. The three eigenvalues μ_i of the 3×3 matrix $\mathbf{B}$ can be derived with the help of Cardan's formula (16):

$$\mu_1 = -\frac{\lambda}{3} + 4\pi R \cos\left(\frac{\phi}{3}\right)$$

$$\mu_{2,3} = -\frac{\lambda}{3} - 4\pi R \cos\left(\frac{\phi \mp \pi}{3}\right) \qquad [8]$$

with

$$\phi = \arccos\left(\frac{-Q}{R^3}\right) \qquad [9]$$

$$Q = \frac{1}{27}[(A - 2\Sigma)(12\Sigma^2 - 36\Delta^2$$
$$\qquad + 9(B^2 + C^2 - D^2) + A^2) - 2\Sigma(2A^2 - 8\Sigma^2)]$$
$$\qquad + 2[\Delta C^2 - \Delta B^2 - BCD] \qquad [10]$$

$$R = \frac{1}{3}\sqrt{(A - 2\Sigma)^2 + 6B^2 + 12\Delta^2 + 6C^2 + 3D^2}. \quad [11]$$

The eigenvalues ν_i of $\mathbf{C}$ can be obtained by solving its quadratic characteristic polynomial

$$\nu_{1,2} = -\lambda \mp 2\pi W \qquad [12]$$

with

$$W = \sqrt{A^2 + 3D^2 + 4\Sigma(\Sigma - A)}. \qquad [13]$$

The eigenvectors of matrix $\mathbf{B}$ can also be solved analytically. For each eigenvalue μ_i the three components α_i, β_i, and γ_i of the corresponding eigenvector can be expressed in terms of the matrix elements B_{lm} defined in Eq. [5],

$$\alpha_i = c_i^{(123)}/n_i; \quad \beta_i = c_i^{(231)}/n_i; \quad \gamma_i = c_i^{(312)}/n_i \quad [14]$$

with

$$c_i^{(lmn)} = B_{mn}(B_{mn} - B_{lm} - B_{ln}) - B_{mm}B_{nn} + B_{mm}B_{ln}$$
$$+ B_{nn}B_{lm} + (B_{mm} - B_{lm} + B_{nn} - B_{ln})\mu_i - \mu_i^2$$

[15]

and the normalization

$$n_i = \sqrt{(c_i^{(123)})^2 + (c_i^{(231)})^2 + (c_i^{(312)})^2}.$$

[16]

This solution for the eigenvectors of matrix $\mathbf{B}$ is general if the three eigenvalues μ_i are nondegenerate. Furthermore it is required that

$$\mu_i \neq B_{mm} - B_{lm} + B_{nn} - B_{ln}$$

[17]

for $\{lmn\} = \{123\}, \{231\}, \{312\}$. With only slight variations of the coupling constants these conditions can always be fulfilled and Eqs. [14]–[16] yield the resulting eigenvector components.

The two components η_i and ζ_i of the eigenvector for each of the eigenvalues ν_i of matrix $\mathbf{C}$ can be expressed as

$$\eta_2 = \zeta_1 = \cos\psi; \quad -\zeta_2 = \eta_1 = \sin\psi$$

[18]

with

$$\psi = \arctan\left(\frac{\sqrt{3}D}{2\Sigma - A + W}\right)$$

[19]

and if $2\Sigma - A + W = 0$ then

$$\psi = \begin{cases} \dfrac{\pi}{2}: & \text{if } D > 0 \\[2mm] -\dfrac{\pi}{2}: & \text{if } D < 0 \end{cases}.$$

[20]

Based on Eqs. [14] and [18] the eigenfunctions $|\psi_k\rangle$ of the isotropic Hamiltonian $\mathcal{H}_{iso}$ can be expressed in terms of the eigenfunctions $|J, m\rangle$ of F^2 and F_z (Table 2).

The eigenfunctions $|\psi_1\rangle, \ldots, |\psi_5\rangle$ correspond to the eigenvalue λ, the eigenfunctions $|\psi_6\rangle$, $|\psi_9\rangle$, and $|\psi_{12}\rangle$ to μ_1, the eigenfunctions $|\psi_7\rangle$, $|\psi_{10}\rangle$, and $|\psi_{13}\rangle$ to μ_2, the eigenfunctions $|\psi_8\rangle$, $|\psi_{11}\rangle$, and $|\psi_{14}\rangle$ to μ_3, and the eigenfunctions $|\psi_{15}\rangle$ and $|\psi_{16}\rangle$ to the eigenvalues ν_1 and ν_2, respectively.

Hence, in the eigenbasis $|\psi_1\rangle, \ldots, |\psi_{16}\rangle$ of $\mathcal{H}_{iso}$, the propagator

$$U_{iso}(\tau) = \exp\{-i\mathcal{H}_{iso}\tau\}$$

[21]

TABLE 2
Eigenfunctions of $\mathcal{H}_{iso}$ Used for Calculations

$|\psi_1\rangle = |2, 2\rangle$
$|\psi_2\rangle = |2, 1\rangle$
$|\psi_3\rangle = |2, 0\rangle$
$|\psi_4\rangle = |2, -1\rangle$
$|\psi_5\rangle = |2, -2\rangle$
$|\psi_6\rangle = \alpha_1|1, 1, 1\rangle + \beta_1|1, 1, 2\rangle + \gamma_1|1, 1, 3\rangle$
$|\psi_7\rangle = \alpha_2|1, 1, 1\rangle + \beta_2|1, 1, 2\rangle + \gamma_2|1, 1, 3\rangle$
$|\psi_8\rangle = \alpha_3|1, 1, 1\rangle + \beta_3|1, 1, 2\rangle + \gamma_3|1, 1, 3\rangle$
$|\psi_9\rangle = \alpha_1|1, 0, 1\rangle + \beta_1|1, 0, 2\rangle + \gamma_1|1, 0, 3\rangle$
$|\psi_{10}\rangle = \alpha_2|1, 0, 1\rangle + \beta_2|1, 0, 2\rangle + \gamma_2|1, 0, 3\rangle$
$|\psi_{11}\rangle = \alpha_3|1, 0, 1\rangle + \beta_3|1, 0, 2\rangle + \gamma_3|1, 0, 3\rangle$
$|\psi_{12}\rangle = \alpha_1|1, -1, 1\rangle + \beta_1|1, -1, 2\rangle + \gamma_1|1, -1, 3\rangle$
$|\psi_{13}\rangle = \alpha_2|1, -1, 1\rangle + \beta_2|1, -1, 2\rangle + \gamma_2|1, -1, 3\rangle$
$|\psi_{14}\rangle = \alpha_3|1, -1, 1\rangle + \beta_3|1, -1, 2\rangle + \gamma_3|1, -1, 3\rangle$
$|\psi_{15}\rangle = \eta_1|0, 0, 1\rangle + \zeta_1|0, 0, 2\rangle$
$|\psi_{16}\rangle = \eta_2|0, 0, 1\rangle + \zeta_2|0, 0, 2\rangle$

Note. The coefficients α_i, β_i, γ_i, η_i, and ζ_i are given in Eqs. [14] and [18].

is a diagonal matrix with the elements $(U)_{11} = (U)_{22} = (U)_{33} = (U)_{44} = (U)_{55} = \exp\{-i\lambda\tau\}$, $(U)_{66} = (U)_{99} = (U)_{1212} = \exp\{-i\mu_1\tau\}$, $(U)_{77} = (U)_{1010} = (U)_{1313} = \exp\{-i\mu_2\tau\}$, $(U)_{88} = (U)_{1111} = (U)_{1414} = \exp\{-i\mu_3\tau\}$, $(U)_{1515} = \exp\{-i\nu_1\tau\}$, and $(U)_{1616} = \exp\{-i\nu_2\tau\}$. The normalized polarization transfer function between two operators A and B is defined as (2)

$$T_{A\rightarrow B}(\tau) = \frac{\text{Tr}\{B^\dagger U(\tau) A U^\dagger(\tau)\}}{\text{Tr}\{B^\dagger B\}}.$$

[22]

With the explicit form of the propagator $U_{iso}(\tau)$ (Eq. [21]) and of the eigenfunctions $|\psi_k\rangle$ (Table 2), the desired polarization transfer functions can be derived in a straightforward way. Compact analytical solutions were found with the help of the algebraic program *Mathematica* (17).

GENERAL RESULTS

The following discussion is focused on polarization transfer functions between I_{kz} and I_{lz} (with $k, l = 1, 2, 3,$ or 4). Except for constant terms, all polarization transfer functions can be expressed as combinations of 12 cosine terms with the oscillation frequencies corresponding to differences of the eigenvalues $|\mu_i - \lambda|$, $|\mu_i - \mu_j|$, and $|\mu_i - \nu_j|$.

In practice, the polarization transfer between two different spins ($k \neq l$) is of particular interest, because it describes the mixing-time dependence of the integrated intensity of the cross peak between the spins k and l. The transfer function $T_{12}(\tau) = T_{I_{1z}\rightarrow I_{2z}}$ between spin $k = 1$ and $l = 2$ can be expressed in the form

$$T_{12}(\tau) = \sum_{i=1}^{3} a_i \{1 - \cos(|\mu_i - \lambda|\tau)\}$$

$$+ \sum_{i<j}^{3} b_{ij} \{1 - \cos(|\mu_i - \mu_j|\tau)\}$$

$$+ \sum_{i=1}^{3} \sum_{j=1}^{2} c_{ij} \{1 - \cos(|\mu_i - \nu_j|\tau)\} \qquad [23]$$

with the coefficients

$$a_i = -\frac{5}{48}(\alpha_i^2 - 2\beta_i^2) \qquad [24]$$

$$b_{ij} = -\frac{\alpha_i \alpha_j (\gamma_i \gamma_j - \beta_i \beta_j)}{4} + \frac{\alpha_i^2 \beta_j^2 + \alpha_j^2 \beta_i^2}{8}$$

$$- \frac{\alpha_i^2 \alpha_j^2}{16} - \frac{\beta_i^2 \beta_j^2}{4} \qquad [25]$$

$$c_{ij} = -\frac{\eta_j^2 (2\alpha_i^2 - \beta_i^2)}{24} - \gamma_i \zeta_j \left(\frac{\beta_i \eta_j}{4\sqrt{3}} - \frac{\gamma_i \zeta_j}{8} \right). \qquad [26]$$

The transfer functions $T_{kl}(\tau)$ for arbitrary $k \neq l$ can be calculated based on Eqs. [23]–[26] if the spin labels of the coupling constants are permuted.

The transfer functions $T_{kk}(\tau)$ that represent the integrated intensities of the diagonal signals can be derived in analogy to the transfer functions $T_{kl}(\tau)$. For example, the transfer function $T_{11}(\tau)$ is given by

$$T_{11}(\tau) = 1 - \sum_{i=1}^{3} a_i' \{1 - \cos(|\mu_i - \lambda|\tau)\}$$

$$- \sum_{i<j}^{3} b_{ij}' \{1 - \cos(|\mu_i - \mu_j|\tau)\}$$

$$- \sum_{i=1}^{3} \sum_{j=1}^{2} c_{ij}' \{1 - \cos(|\mu_i - \nu_j|\tau)\} \qquad [27]$$

with the coefficients

$$a_i' = \frac{5}{48}(\alpha_i + \sqrt{2}\beta_i)^2 \qquad [28]$$

$$b_{ij}' = \frac{1}{4} \left(\frac{\alpha_i \alpha_j}{2} + \gamma_i \gamma_j - \frac{\alpha_i \beta_j}{\sqrt{2}} - \frac{\alpha_j \beta_i}{\sqrt{2}} \right)^2 \qquad [29]$$

$$c_{ij}' = \frac{1}{4} \left(\frac{\alpha_i \eta_j}{\sqrt{3}} + \frac{\gamma_i \zeta_j}{\sqrt{2}} - \frac{\beta_i \eta_j}{\sqrt{6}} \right)^2. \qquad [30]$$

Again, for arbitrary k the transfer functions $T_{kk}(\tau)$ can be obtained by Eqs. [27]–[30] by a permutation of the spin labels.

SPECIAL CASES

The general solution presented is valid for all four-spin systems with nondegenerate eigenvalues μ_i (cf. Eqs. [8] and [12]) and the restrictions of Eq. [17]. In this section we will discuss some special coupling topologies with simplified coherence transfer functions (cf. Fig. 1).

The special case of an effective AMX$_2$-type spin system is shown in Fig. 1a. In this case the spins 3 and 4 are magnetically equivalent as $J_{13} = J_{14}$ and $J_{23} = J_{24}$. Since coherence transfer functions do not depend on the coupling constant between the two equivalent spins 3 and 4, J_{34} is set to zero without loss of generality (18). In this case the polarization transfer functions simplify according to the reduced block structure of the Hamiltonian. The submatrix **B** of Eq. [5] consists of a 2×2 and a 1×1 block

$$\mathbf{B}^{(a)} = \frac{\pi}{2} \begin{pmatrix} J_{12} - 2J_{13} - 2J_{23} & \sqrt{8}(J_{23} - J_{13}) & 0 \\ \sqrt{8}(J_{23} - J_{13}) & -3J_{12} & 0 \\ 0 & 0 & J_{12} \end{pmatrix}$$

$$[31]$$

and the matrix **C** of Eq. [6] is diagonal

$$\mathbf{C}^{(a)} = \frac{\pi}{2} \begin{pmatrix} J_{12} - 4J_{13} - 4J_{23} & 0 \\ 0 & -3J_{12} \end{pmatrix}. \qquad [32]$$

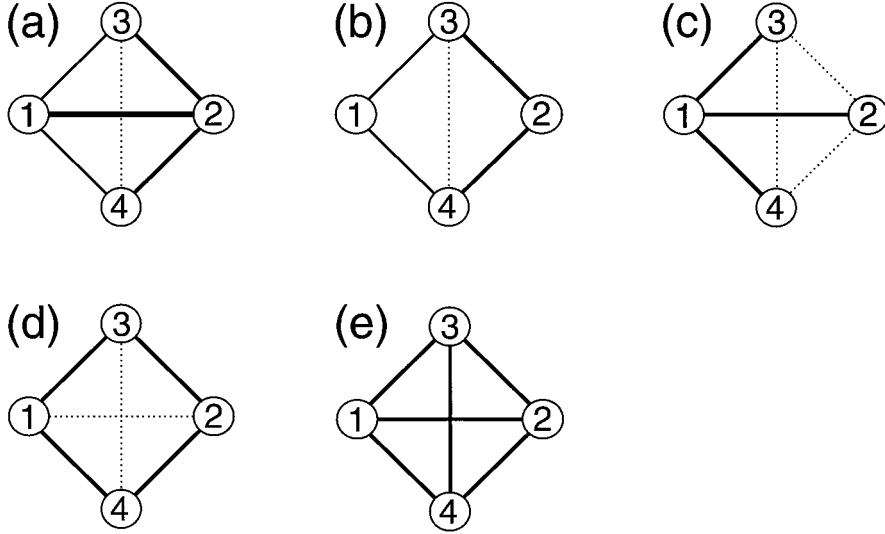The resulting eigenvalues of the Hamiltonian of the effective AMX$_2$-type spin system are

$$\lambda^{(a)} = \frac{\pi}{2}(J_{12} + 2J_{13} + 2J_{23}) = \mathbf{A}^{(a)}$$

$$\mu_{1,2}^{(a)} = \frac{\pi}{2}(-J_{12} - J_{13} - J_{23} \mp W^{(a)})$$

$$\mu_3^{(a)} = \frac{\pi}{2} J_{12}$$

$$\nu_1^{(a)} = \frac{\pi}{2}(J_{12} - 4J_{13} - 4J_{23})$$

$$\nu_2^{(a)} = -\frac{3\pi}{2} J_{12} \qquad [33]$$

FIG. 1. In addition to the general case with arbitrary coupling constants five different special coupling topologies of a spin system consisting of four spins $\frac{1}{2}$ are discussed (see text): the general effective AMX_2-type spin system (a), the effective linear AM_2X-type spin system (b), the AX_3-type spin system (c), the A_2X_2-type spin system (d), and the equally coupled four-spin system (e). Equal coupling constants are shown with equal line thickness. Dotted lines represent coupling constants between magnetically equivalent spins.

with

$$W^{(a)} = \sqrt{(2J_{12} - J_{13} - J_{23})^2 + 8(J_{13} - J_{23})^2}. \quad [34]$$

The components of the eigenvectors of the 2×2 block of the matrix $\mathbf{B}^{(a)}$ are

$$\alpha_1^{(a)} = \beta_2^{(a)} = \cos \psi^{(a)}; \quad -\alpha_2^{(a)} = \beta_1^{(a)} = \sin \psi^{(a)} \quad [35]$$

with the mixing angle

$$\psi^{(a)} = \arctan\left(\frac{\sqrt{8}(J_{23} - J_{13})}{2J_{12} - J_{13} - J_{23} - W^{(a)}}\right). \quad [36]$$

The resulting polarization transfer functions have a form similar to that of the general polarization transfer functions (Eqs. [23] and [27])

$$T_{kl}^{(a)}(\tau) = \sum_{i=1}^{2} d_i\{1 - \cos(|\mu_i^{(a)} - \lambda^{(a)}|\tau)\}$$

$$+ e_{12}\{1 - \cos(|\mu_1^{(a)} - \mu_2^{(a)}|\tau)\}$$

$$+ \sum_{i=1}^{3} \sum_{j=1}^{2} f_{ij}\{1 - \cos(|\mu_i^{(a)} - \nu_j^{(a)}|\tau)\} \quad [37]$$

$$T_{kk}^{(a)}(\tau) = 1 - \sum_{i=1}^{2} d_i\{1 - \cos(|\mu_i^{(a)} - \lambda^{(a)}|\tau)\}$$

$$- e_{12}\{1 - \cos(|\mu_1^{(a)} - \mu_2^{(a)}|\tau)\}$$

$$- \sum_{i=1}^{3} \sum_{j=1}^{2} f_{ij}\{1 - \cos(|\mu_i^{(a)} - \nu_j^{(a)}|\tau)\} \quad [38]$$

but with only six nonvanishing coefficients d_1, d_2, e_{12}, f_{21}, f_{22}, and f_{32} shown in Table 3 for the polarization transfer functions $T_{11}^{(a)}$, $T_{(34)(34)}^{(a)}$, $T_{12}^{(a)}$, and $T_{1(34)}^{(a)}$, where (34) indicates the pair of effectively equivalent spins (for example, $T_{1(34)}^{(a)} = T_{I_{1z} \to (I_{3z} + I_{4z})}^{(a)}$). The polarization transfer functions $T_{22}^{(a)}$ and $T_{2(34)}^{(a)}$ are obtained from $T_{11}^{(a)}$ and $T_{1(34)}^{(a)}$ by a simple permutation of the spin labels of the coupling constants.

If $J_{12} = 0$ an effective linear AM_2X-type spin system results (Fig. 1b) which is of interest for spin systems containing a methylene group. The polarization transfer functions for this case are derived from the effective AMX_2-type spin system by simply setting $J_{12} = 0$. As a result the eigenvalues $\mu_3^{(b)}$ and $\nu_2^{(b)}$ vanish as well as the coefficient f_{32} of the polarization transfer functions.

The analytical solutions for the effective AX_3-type coupling topology with three magnetically equivalent spins 2, 3, and 4 and for the A_2X_2-type coupling topology with magnetically equivalent spins 1, 2 and 3, 4, respectively, were derived in (11). The coupling constants for the AX_3-type spin system are $J_{12} = J_{13} = J_{14} = J$. Since the coherence transfer functions

TABLE 3
Amplitudes of the Harmonic Components of the Effective AMX$_2$-Type Spin System (cf. Eqs. [33]–[38])

	d_i ($i = 1, 2$)	e_{12}	f_{i1} ($i = 1, 2$)	f_{32}
$T_{11}^{(a)}$	$\frac{5}{48}(\alpha_i^{(a)} + \sqrt{2}\beta_i^{(a)})^2$	$\frac{1}{16}(\sqrt{2}\alpha_2^{(a)}\beta_1^{(a)} + \sqrt{2}\alpha_1^{(a)}\beta_2^{(a)} - \alpha_1^{(a)}\alpha_2^{(a)})^2$	$\frac{1}{24}(\sqrt{2}\alpha_i^{(a)} - \beta_i^{(a)})^2$	$\frac{1}{8}$
$T_{(34)(34)}^{(a)}$	$\frac{5}{24}\alpha_i^{(a)2}$	$\frac{1}{8}(\alpha_2^{(a)}\alpha_1^{(a)} + 2\beta_2^{(a)}\beta_1^{(a)})^2$	$\frac{1}{6}\alpha_i^{(a)2}$	0
$T_{12}^{(a)}$	$\frac{5}{48}(2\beta_i^{(a)2} - \alpha_i^{(a)2})$	$\frac{1}{8}(\alpha_1^{(a)}\beta_2^{(a)} + \alpha_2^{(a)}\beta_1^{(a)})^2 - \frac{1}{16}\alpha_2^{(a)2}\alpha_1^{(a)2}$	$\frac{1}{24}(\beta_i^{(a)2} - 2\alpha_i^{(a)2})$	$\frac{1}{8}$
$T_{1(34)}^{(a)}$	$\frac{5}{48}(\alpha_i^{(a)2} + \sqrt{2}\alpha_i^{(a)}\beta_i^{(a)})$	$-\frac{1}{16}(\alpha_2^{(a)}\alpha_1^{(a)} + 2\beta_2^{(a)}\beta_1^{(a)})(\eta_2^{(a)}\eta_1^{(a)} - \sqrt{2}\eta_2^{(a)}\zeta_1^{(a)} - \sqrt{2}\eta_1^{(a)}\zeta_2^{(a)})$	$\frac{\sqrt{2}}{24}(\sqrt{2}\eta_i^{(a)2} - \eta_i^{(a)}\zeta_i^{(a)})$	0

Note. $f_{12} = f_{22} = f_{31} = 0$.

do not depend on the coupling constants between the magnetically equivalent spins 2, 3, and 4 we may also set $J_{23} = J_{24} = J_{34} = J$ without loss of generality (cf. Fig. 1c). In this case the spin topology is reduced to the spin system consisting of four equally coupled spins (cf. Fig. 1e) with the coupling constants $J_{12} = J_{13} = J_{14} = J_{23} = J_{24} = J_{34} = J$. The Hamiltonian of the equally coupled four-spin system is already diagonal and the polarization transfer functions are

$$T_{kl}^{(e)} = T_{12}^{(e)} = \tfrac{1}{12}\{1 - \cos(2\pi J\tau)\}$$

$$+ \tfrac{5}{48}\{1 - \cos(4\pi J\tau)\} \quad [39]$$

$$T_{kk}^{(e)} = T_{11}^{(e)} = 1 - \tfrac{1}{4}\{1 - \cos(2\pi J\tau)\}$$

$$- \tfrac{5}{16}\{1 - \cos(4\pi J\tau)\}. \quad [40]$$

Summation of the polarization transfer functions of spin 1 to spins 2, 3, 4 yields the results for the AX$_3$-type polarization transfer functions $3T_{1(234)}^{(c)} = T_{(234)1}^{(c)} = T_{21}^{(e)} + T_{31}^{(e)} + T_{41}^{(e)} = 3T_{12}^{(e)}$, $T_{11}^{(c)} = T_{11}^{(e)}$, and $T_{(234)(234)}^{(c)} = \tfrac{1}{3}\{T_{22}^{(e)} + T_{33}^{(e)} + T_{44}^{(e)} + T_{23}^{(e)} + T_{32}^{(e)} + T_{24}^{(e)} + T_{42}^{(e)} + T_{34}^{(e)} + T_{43}^{(e)}\} = T_{11}^{(e)} + 2T_{12}^{(e)}$. With the normalization conditions defined by Eq. [22] the summation leads to

$$T_{1(234)}^{(c)} = \tfrac{1}{12}\{1 - \cos(2\pi J\tau)\} + \tfrac{5}{48}\{1 - \cos(4\pi J\tau)\}$$

$$[41]$$

$$T_{(234)1}^{(c)} = \tfrac{1}{4}\{1 - \cos(2\pi J\tau)\} + \tfrac{5}{16}\{1 - \cos(4\pi J\tau)\}l$$

$$[42]$$

$$T_{11}^{(c)} = 1 - T_{(234)1}^{(c)} = 1 - \tfrac{1}{4}\{1 - \cos(2\pi J\tau)\}$$

$$- \tfrac{5}{16}\{1 - \cos(4\pi J\tau)\} \quad [43]$$

$$T_{(234)(234)}^{(c)} = 1 - T_{1(234)}^{(c)} = 1 - \tfrac{1}{12}\{1 - \cos(2\pi J\tau)\}$$

$$- \tfrac{5}{48}\{1 - \cos(4\pi J\tau)\} \quad [44]$$

in agreement with (*11*).

The polarization transfer functions for the A$_2$X$_2$-type spin system (cf. Fig. 1d) can be derived in the same way. The coupling constants are $J_{13} = J_{14} = J_{23} = J_{24} = J$. Again without loss of generality the coupling constants J_{12} and J_{34} of the magnetically equivalent spin pairs are set to J to reduce the topology to the equally coupled four-spin system. Using $T_{(12)(34)}^{(d)} = \tfrac{1}{2}\{T_{13}^{(e)} + T_{14}^{(e)} + T_{23}^{(e)} + T_{24}^{(e)}\} = 2T_{12}^{(e)}$ and $T_{(34)(34)}^{(d)} = 1 - T_{(12)(34)}^{(d)} = \tfrac{1}{2}\{T_{33}^{(e)} + T_{44}^{(e)} + T_{34}^{(e)} + T_{43}^{(e)}\} = T_{11}^{(e)} + T_{12}^{(e)}$ and the normalization condition defined by Eq. [22] the polarization transfer functions result in (*11*)

$$T_{(12)(34)}^{(d)} = T_{(34)(12)}^{(d)} = \tfrac{1}{6}\{1 - \cos(2\pi J\tau)\}$$

$$+ \tfrac{5}{24}\{1 - \cos(4\pi J\tau)\} \quad [45]$$

$$T_{(12)(12)}^{(d)} = T_{(34)(34)}^{(d)} = 1 - \tfrac{1}{6}\{1 - \cos(2\pi J\tau)\}$$

$$- \tfrac{5}{24}\{1 - \cos(4\pi J\tau)\}. \quad [46]$$

EXPERIMENTS

In order to verify the analytical polarization transfer functions, experimental transfer functions were acquired for *trans*-phenylcyclopropane carboxylic acid (*19*). The coupling constants of the ^{1}H spin system are $J_{12} = 4.1$ Hz, $J_{13} = 9.4$ Hz, $J_{14} = 6.8$ Hz, $J_{23} = 5.3$ Hz, $J_{24} = 8.2$ Hz, and $J_{34} = -4.6$ Hz. After selective excitation of the first spin isotropic mixing conditions were created using the DIPSI-2 sequence (*29*). A set of 1D experiments with incremented isotropic mixing periods was recorded. Each increment corresponds to a complete DIPSI-2 cycle of duration $\tau_{cyc} = 5.76$ ms. From these experiments the experimental polarization transfer functions have been extracted by using the integrated intensities as functions of the mixing time τ. The results for $T_{11}(\tau)$, $T_{12}(\tau)$, $T_{13}(\tau)$, and $T_{14}(\tau)$ are shown in Fig. 2.

The theoretical polarization transfer functions of *trans*-phenylcyclopropane carboxylic acid were calculated using the general results of Eqs. [23] and [27], respectively. The amplitudes of the 12 frequency components are summarized in Table 4. Although all harmonical components are nonzero only about half of the frequency components contribute significantly to the
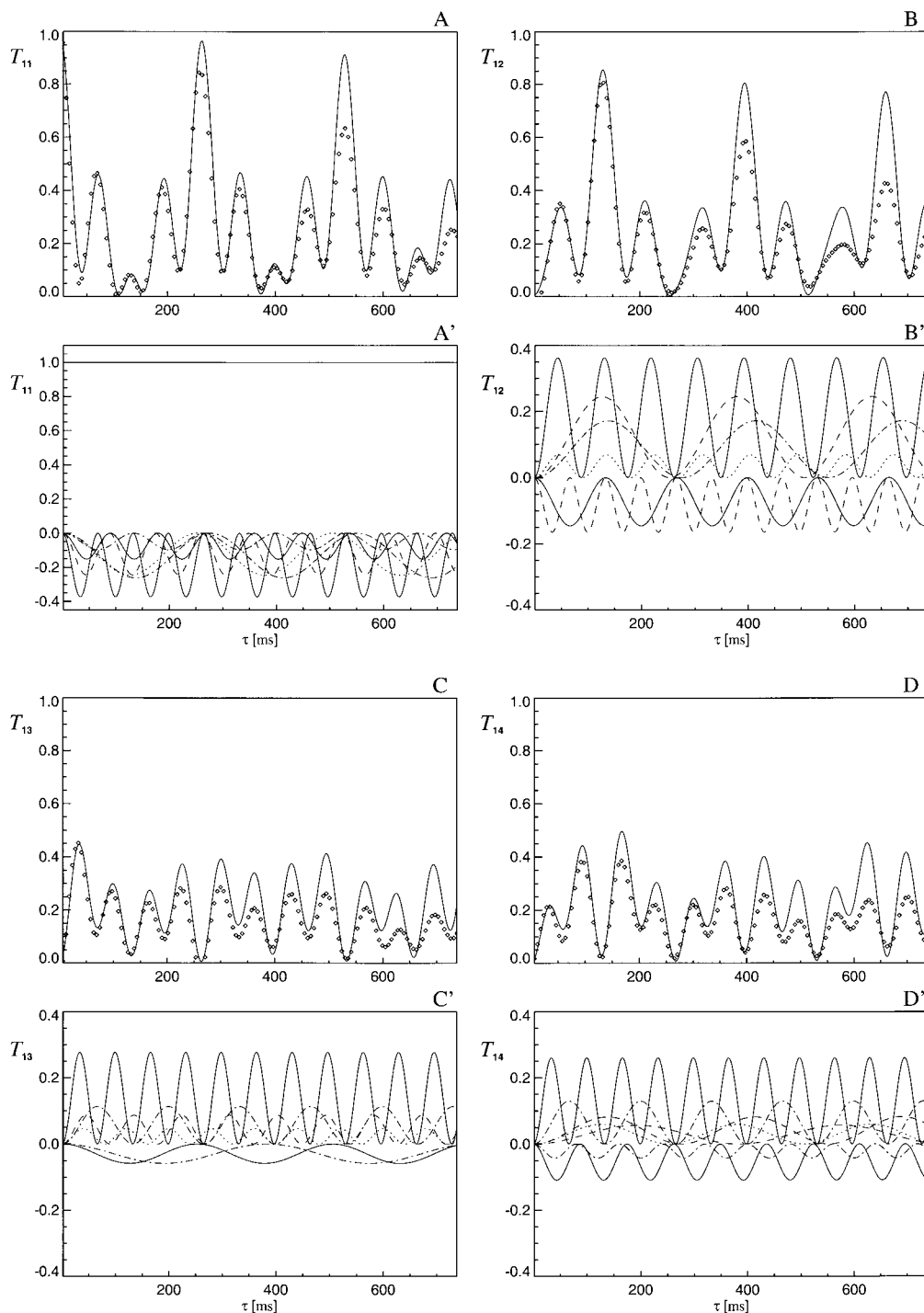
FIG. 2. For the ^{1}H spin system of *trans*-phenylcyclopropane carboxylic acid with $J_{12} = 4.1$ Hz, $J_{13} = 9.4$ Hz, $J_{14} = 6.8$ Hz, $J_{23} = 5.3$ Hz, $J_{24} = 8.2$ Hz, and $J_{34} = -4.6$ Hz (*19*), the theoretical (solid curves) and experimental (diamonds) transfer functions (A) $T_{11}(\tau)$, (B) $T_{12}(\tau)$, (C) $T_{13}(\tau)$, and (D) $T_{14}(\tau)$ are shown for isotropic mixing conditions. The experimental transfer functions were extracted from a series of 1D experiments in which the selective excitation of spin 1 was followed by an isotropic mixing period of increasing duration. In A′ to D′ the main frequency components of the transfer functions are shown (cf. underlined coefficients in Table 4).

polarization transfer functions (underlined coefficients in Table 4).

Figures 2A–2D show the experimental and theoretical po-

larization transfer functions $T_{11}(\tau)$, $T_{12}(\tau)$, $T_{13}(\tau)$, and $T_{14}(\tau)$, respectively. Since relaxation was not taken into consideration in the theoretical transfer functions the correspondence be-

TABLE 4
Calculated Coefficients of the Frequency Components of the Polarization Transfer Functions for the Four-Spin System of *trans*-Phenylcyclopropane Carboxylic Acid

	T_{11}	T_{12}	T_{13}	T_{14}	Frequency
$a_1^{()}$	0.004080	0.004929	−0.029223	0.028373	16.3847
$a_2^{()}$	0.121756	0.181430	−0.005243	−0.054430	72.1458
$a_3^{()}$	0.186664	−0.082193	0.138634	0.130224	94.9386
$b_{12}^{()}$	0.130910	0.085895	0.004187	0.040827	22.7928
$b_{13}^{()}$	0.002861	−0.005151	−0.000882	0.008895	55.7611
$b_{23}^{()}$	0.004386	0.002333	0.023335	−0.021282	78.5539
$c_{11}^{()}$	0.123135	0.122509	−0.029244	0.029870	24.8581
$c_{21}^{()}$	0.000179	0.000486	0.004240	−0.004547	30.9030
$c_{31}^{()}$	0.048648	−0.072729	0.056643	0.064733	47.2877
$c_{12}^{()}$	0.001685	−0.001739	0.005487	−0.002062	53.6958
$c_{22}^{()}$	0.076118	0.034393	0.043375	−0.001650	70.0805
$c_{32}^{()}$	0.000233	0.000413	0.002830	−0.003009	125.8420

Note. For T_{11} the coefficients correspond to $a_1' - c_{32}'$ of Eqs. [27] to [30]. For T_{12}, T_{13}, and T_{14} the coefficients correspond to $a_1 - c_{32}$ of Eqs. [23] to [26]. T_{13} and T_{14} are derived from Eqs. [23] to [26] by a permutation of the spin labels. The given frequencies correspond to $|\mu_i - \lambda|$ for $a_i^{()}$, to $|\mu_i - \mu_j|$ for $b_{ij}^{()}$, and to $|\mu_i - \nu_j|$ for $c_{ij}^{()}$.

tween theory and experiment is quite satisfactory. Figures 2A′–2D′ show the main harmonic components (underlined prefactors in Table 4) which contribute to the theoretical transfer functions.

DISCUSSION

Analytical polarization transfer functions were derived for the general case of four isotropically coupled spins $\frac{1}{2}$ with arbitrary coupling constants J_{ij}, $i < j \leq 4$, and for the special cases of AMX_2-type and linear AM_2X-type effective coupling topologies. In addition it is shown that the AX_3-type and the A_2X_2-type spin systems can be reduced to the case of four identically coupled spins for which a general solution was derived. The transfer functions can be useful for the determination of optimal mixing times in TOCSY experiments of four-spin systems. This is quite significant since it has been demonstrated previously in applications to amino acids (*4*) that the simple two-spin approximation can yield extremely inaccurate estimates of the ideal mixing time in more complex spin systems. The transfer functions presented correspond to the ideal isotropic mixing case where experimental imperfections and relaxation are neglected. In order to estimate optimal mixing times for practical applications, the transfer functions should be multiplied with an appropriate damping function (*20*).

For homonuclear Hartmann–Hahn mixing sequences such as CW irradiation (*21*) or MLEV-17 (*22*) where a nonzero effective spin-lock field is created, the effective Hamiltonian contains a term $\mathcal{H}_{SL} = 2\pi\nu_{eff}F_x$ in addition to the isotropic mixing term $\mathcal{H}_{iso}$. Since $\mathcal{H}_{SL}$ commutes with $\mathcal{H}_{iso}$ and with $I_{i,x}$ the transfer functions in Table 2 still apply if the axis labels x, y, and z are replaced by y, z, and x, respectively.

Although isotropic mixing experiments are commonly associated with homonuclear spin systems, they can also be of advantage in heteronuclear coherence transfer experiments (*2, 23–28*) for efficient in-phase coherence order-selective coherence transfer, albeit with a reduction of the effective coupling constants by a factor of $\frac{1}{3}$. If this scaling factor is taken into account, the transfer functions derived also apply to the case of heteronuclear isotropic mixing experiments in which both homonuclear and heteronuclear spins are effectively isotropically coupled.

Under isotropic mixing conditions negative coherence transfer has been found only for spin systems consisting of more than four spins $\frac{1}{2}$ (*3*). For the general three-spin system it could be shown in (*10*) that the polarization transfer functions under isotropic mixing conditions are always positive. However, the conjecture (*3*) that coherence transfer functions are also positive for all four-spin systems under isotropic mixing conditions could not be proven so far. Possibly the analytical solutions presented in this paper may form the basis of such a proof.

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