Table IV. Geometric Relationships and Estimated Interaction Energies of the Dipoles of the Peptide Bond and the Indole Ring in Spin-Labeled Methyl L-Tryptophanate[a]

conformer	angle, deg	dipole–dipole sepn, Å	dipolar energy,[b] kcal/mol	fraction[c]
A	35	4.83	+0.73	0.02
B	120	5.10	-0.34	
C	121	4.93	-0.56	0.98

[a] Calculated for point dipoles, as described in 3-methylindole[24] and for the peptide bond.[22,23] [b] Calculated for the molecule in vacuo. [c] Calculated at -100 °C to approximate the freezing temperatures[21] of the solvents employed; conformer B is not included in the estimation of relative conformer populations because no spectroscopic evidence was observed for its existence in chloroform/toluene, as discussed in the text.

and the spin-labeled tryptophanate molecule must be of importance in conformer stabilization.

We suggest that the solvent dependence of the relative populations of the two conformers can be explained in terms of the interactions of the dipole moment of the peptide bond with that of the indole ring. It is well-known that the peptide bond is associated with a strong electric dipole moment of approximately 3.7 D.[22,23] Experimental and theoretical determinations of the value and direction in the dipole moments of indole and of its derivatives[24-26] have shown that the net dipole moment of the indole ring of 2.13 D is directed from the center of the $C^{\epsilon 2}$–$C^{\delta 2}$ bond toward $N^{\epsilon 1}$ (see Figure 1 for atom labeling), with the nitrogen associated with the positive end of the dipole. Applying the dipoles as described for 3-methylindole[24] and the peptide bond,[22] we have estimated their interaction energies for the conformers illustrated in Figure 7. The results are summarized in Table IV. For conformer C the two dipoles are oriented approximately antiparallel, while in conformer A the dipoles are more nearly parallel. Based on the calculated dipolar interaction energy alone, conformer C is, thus, expected to be of greater population. On the other hand, the unfavorable dipolar interaction energy calculated for conformer A will be effectively reduced through hydrogen-bonding interactions of the indole ring and peptide group with methanol or through the higher dielectric screening effect of methanol over that of chloroform/toluene. On this basis, both conformers A and C may be expected to be present in methanol, as is, indeed, observed. It is of interest also to note that by calculation conformer B would be favored by the indole–peptide dipolar interaction in a solvent of low dielectric constant. The absence of a detectable fraction of this conformer in chloroform/toluene that would be characterized by an approximate 10-Å electron–fluorine separation (cf., Table II) supports our conclusion made earlier that conformer B is energetically unfavorable relative to conformers A and C.

Registry No. I, 125250-24-0; unlabeled I, 106367-36-6; II, 125250-25-1; III, 125250-26-2; IV, 125250-27-3; V, 125250-28-4; VI, 125250-29-5; VII, 125250-30-8; VIII, 125250-31-9; H-D-Trp-OH, 153-94-6; Ac-DL-(α-^{2}H)Trp-OH, 80525-43-5; H-(α-^{2}H)Trp-OH, 81279-11-0; H-Trp-OMe·HCl, 7524-52-9; 2,2,5,5-tetramethyl-1-oxypyrroline-3-carboxylic acid, 2154-67-8.

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Elimination of Cross-Relaxation Effects from Two-Dimensional Chemical-Exchange Spectra of Macromolecules

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Abstract: We demonstrate here a method for eliminating cross-relaxation effects from exchange spectra of macromolecules that permits a more rigorous study of chemical-exchange processes. In the spin diffusion limit, the laboratory-frame cross-relaxation rate is negative and equal to half the rotating-frame cross-relaxation rate, which is positive. If, during the mixing time, the magnetization is flipped rapidly between the two frames such that the average residence time in the NOESY:ROESY frames is 2:1, then the magnetization exchange due to cross-relaxation will cancel out and be removed. Since chemical exchange takes place steadily, irrespective of the frame of reference, it will contribute to cross-peak volumes in the usual manner. This approach has been applied to the elimination of cross-relaxation effects from the 2D exchange spectrum of a small globular protein, turkey ovomucoid third domain (6062 Da). The results demonstrate that tyrosine-31 executes ring flips on the millisecond time scale.

Two-dimensional (2D) exchange spectroscopy[1,2] has become a popular method for investigating molecular structure and dynamics. The method provides information on incoherent magnetization transfer among spins due to chemical exchange and cross-relaxation. These two processes are independent and can occur simultaneously. In order to analyze 2D exchange spectra, one needs to distinguish and evaluate the magnetization transfer that occurs by these two different mechanisms. In NOESY spectra of macromolecules, cross-relaxation and chemical exchange are indistinguishable because they both give rise to positive cross-peaks.[3] In ROESY spectra of macromolecules direct

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cross-relaxation and exchange can be distinguished since cross-peaks from the former are negative with respect to the diagonal, whereas those of the latter are positive.[4] However, since two-step magnetization transfer (spin diffusion) in ROESY spectra also gives rise to positive cross-peaks, the presence of such peaks is not diagnostic for exchange in cases where the mixing time necessary for observing chemical exchange is of the same order as that for two-step cross-relaxation. This condition occurs frequently in NMR spectra of biomacromolecules. We introduce here a method for eliminating cross-relaxation effects from 2D exchange spectra of macromolecules. Our method, which is analogous to those reported for the elimination of cross-relaxation from TOCSY or HOHAHA spectra,[5,6] permits quantitative evaluation of magnetization exchange rates in the presence of cross-relaxation.

For rigid-body isotropic motion in macromolecules, where $\omega_0\tau_c \gg 1$, the ratio of the longitudinal to transverse cross-relaxation rates, σ^n/σ^r, is equal to $-1/2$,[7] When the mixing period of an exchange experiment is designed so that the magnetization components alternately cross-relax along the longitudinal axis and the transverse axis, with the time period along the longitudinal axis twice as long as that along the transverse axis, the direct cross-relaxation peaks will cancel. An appropriate mixing pulse sequence can be derived by interleaving the NOESY and ROESY mixing periods:

$$\tau^n\text{–}(90°)_y\text{–}(\tau^r, \text{spin lock})_x\text{–}(90°)_{-y}\text{–}\tau^n\text{–}(90°)_x\text{–}(\tau^r, \text{spin lock})_y\text{–}(90°)_{-x} \quad \text{(A)}$$

By contrast, the chemical exchange cross peaks, which are not affected by such a pulse sequence,[2] will survive the mixing period and be detected.

For a sufficiently short mixing period, τ_m, the volume of the cross-relaxation cross-peak between spins k and l, $a_{kl}(\tau_m)$, is given by[3,8]

$$\frac{a_{kl}(\tau_m)}{n_k a_{ll}(0)} = -\sigma_{kl}\tau_m + \tfrac{1}{2}\sum_{j\neq k,l} n_j\sigma_{kj}\sigma_{jl}\tau_m^2 \quad (1)$$

where n_k is the number of spins at site k and $a_{ll}(0)$ is the volume of the diagonal cross-peak for $\tau_m = 0$. The summation goes over all neighboring spins, including k and l, with which the observed spins k and l can cross-relax. Uniform compensation of cross-relaxation in the laboratory and rotating frames will be achieved only if the ratio of cross-peak volumes, a_{kl}, depends on the corresponding cross-relaxation rates $\sigma_{kl}^{n,r}$ alone and not on the other possible cross-relaxation pathways, $\sigma_{jk}^{n,r}$ or $\sigma_{jl}^{n,r}$. Suppression of two-step transfer, therefore, can be realized by choosing very short mixing times, $\tau_m^{n,r}$. For very short time periods, precession due to chemical shift is small, and therefore spin locking during the τ^r period can be omitted so that the mixing pulse sequence (A) becomes

$$\tau^n\text{–}(90°)_y\text{–}\tau^r\text{–}(90°)_{-y}\text{–}\tau^n\text{–}(90°)_x\text{–}\tau^r\text{–}(90°)_{-x} \quad \text{(B)}$$

This sequence is very similar to the Waugh–Huber–Haeberlen sequence,[9] which is used to keep magnetization at the magic angle, $\theta = \arccos(1/3)^{1/2}$. In sequence B the corresponding angle is $\beta = 90° - \theta = \arctan(1/2)^{1/2}$ when net magnetization exchange due to cross-relaxation is zero, eq 2 (vide infra). The cross-relaxation rate between spins k and l in an effective spin-locking field that makes an angle $\beta_{k,l}$ with the z axis is[10,11]

$$\sigma_{kl}^{\text{eff}} = \sigma_{kl}^n \cos\beta_k \cos\beta_l + \sigma_{kl}^r \sin\beta_k \sin\beta_l \quad (2)$$

Cosine and sine terms from eq 2 that represent the projections of the effective spin-locking fields onto longitudinal and transverse directions can be replaced by the fractions of time the total magnetization spends in the two frames during the mixing period of sequence B. During this sequence, the effective cross-relaxation rate is a time average of the longitudinal, σ^n, and transverse, σ^r, cross-relaxation rates (eq 3).[5,6] τ^r and τ^n are the times that the

$$\sigma_{kl}^{\text{eff}} = \frac{\tau^r}{\tau^n + \tau^r}\sigma_{kl}^r + \frac{\tau^n}{\tau^n + \tau^r}\sigma_{kl}^n \quad (3)$$

magnetization spends in the rotating and laboratory frames, respectively. The time spent in the rotating frame in the absence of an rf field must be kept short compared to the reciprocal of the chemical shift difference (Hz) for the cross-relaxing resonances. Since the time for flipping from one frame to the other (t_{90}) is not negligible compared to the overall time spent in either frame, i.e., $\tau^{n,r} \sim t_{90}$, cross-relaxation during the pulse must be taken into account. If off-resonance effects are neglected, cross-relaxation during a pulse contributes equally to longitudinal and transverse magnetization.[5,12] The total average cross-relaxation times spend in the two frames are $\tau^n + t_{90}$ and $\tau^r + t_{90}$. From eq 2 one obtains

$$\sigma_{kl}^{\text{eff}} = \frac{\tau^r + t_{90}}{\tau^n + \tau^r + 2t_{90}}\sigma_{kl}^r + \frac{\tau^n + t_{90}}{\tau^n + \tau^r + 2t_{90}}\sigma_{kl}^n \quad (4)$$

The ratio of the cross-relaxation rates is then

$$\frac{\sigma^n}{\sigma^r} = \frac{\tau^r + t_{90}}{\tau^n + t_{90}} \quad (5)$$

In macromolecules, $\sigma^n/\sigma^r = -1/2$; thus the required relationship among τ^n, τ^r, and t_{90} needed to suppress cross-relaxation is

$$\tau^n = 2\tau^r + t_{90} \quad (6)$$

The procedure was applied to the study of the slow ring flip of tyrosine-31 in turkey ovomucoid third domain (OMTKY3, 6062 Da). Tyrosine at this position is conserved in a wide range of Kazal inhibitors and apparently plays a key role in stabilizing the domain structure.[13] We have obtained NOESY and ROESY data for OMTKY3 at 5 °C (Figures 1 and 2). Chemical exchange cross-peaks between the tyrosine-31 ϵ_1 and ϵ_2 protons (at 7.80 and 6.65 ppm) and δ_1 and δ_2 protons (at 7.27 and 6.95 ppm) are observed in both NOESY (Figure 1A) and ROESY (Figure 1B) spectra.[14] In the NOESY spectrum (Figure 1A), all peaks are positive, and no distinction can be made among chemical exchange, direct cross-relaxation, and spin diffusion cross-peaks. In the ROESY spectrum (Figure 1B), negative cross-peaks clearly indicate direct cross-relaxation while positive cross-peaks can be from either chemical exchange or spin diffusion. However, in the pure chemical-exchange spectrum recorded by pulse sequence B (Figures 1C and 2C), all cross-peaks due to cross-relaxation are

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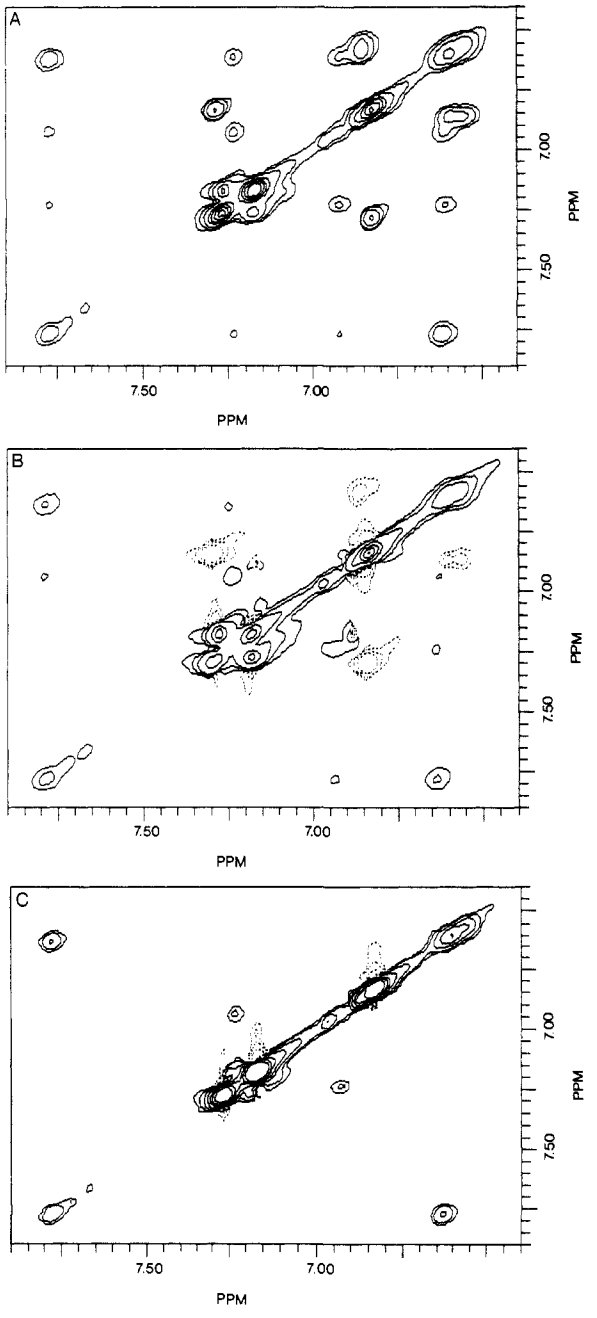

Figure 1. Comparison of the aromatic region from three 2D cross-relaxation spectra of turkey ovomucoid third domain (OMTKY3): (A) NOESY spectrum obtained with τ_m = 120 ms, (B) ROESY spectrum obtained with a 13-kHz rf field and 60-ms spin lock, (C) pure chemical-exchange spectrum collected by using proposed pulse sequence B. Conditions for the pulse sequence were as follows: 65 μs of laboratory-frame cross-relaxation (τ^n), 19 μs for a 90° pulse (t_{90}), and 20 μs of free precession (τ^r), with cycling 488 times in order to obtain the total mixing time of 120 ms. Sample conditions were as follows: protein concentration, 15 mM in ^2H_2O; pH* = 8.1; temperature, 5 °C. All data were collected at 500 MHz on a Bruker AM-500 spectrometer with 512 t_1 increments and 2048 t_2 data points (covering a range of 11 ppm). Squared, shifted, sine-bell multiplications was performed in both domains with a phase shift of $\pi/4$. Cross-peaks that are negative with respect to the diagonal are indicated by dashed lines.

eliminated and only cross-peaks due to chemical exchange remain. Even peaks A and B (Figure 2), which are apparently due to spin diffusion, are canceled.

To achieve $\tau^r/\tau^n = 1/2$ with τ^r = 20 μs and t_{90} = 19 μs, eq 5 requires that $\tau^n = 2.95\tau^r$. Experimentally, however, we observed that cross-relaxation is canceled at $\tau^n = 3.25\tau^r$. Computer simulations of two-spin cross-relaxations during this mixing sequence suggest that effects due to resonance offset and B_1 field inhomogeneity contribute to an underestimation of the required τ^n.

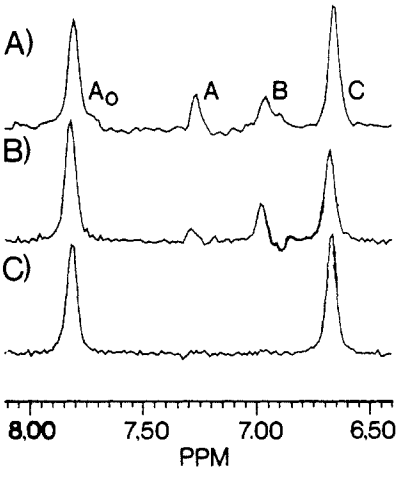

Figure 2. Cross sections, parallel to ω_2 through the diagonal resonance of the tyrosine-31 $H^{\epsilon 1}$, derived from the three phase-sensitive 2D experiments shown in Figure 2. (A) NOESY: peak A_0 is the diagonal peak, cross-peaks A and B are due to spin diffusion, cross-peak C is due to chemical exchange. (B) ROESY. (C) Pure chemical exchange.

In order to compensate for these two effects we have investigated the mixing pulse sequence

$$\tau^n\text{–}(360°)_x\text{–}(360°)_{-x} \qquad \text{(C)}$$

The delay time, τ^n, during which longitudinal cross-relaxation occurs, is followed by an approximate cyclic pulse consisting of two sequential 360° pulses with opposite phases,[16] during which time both longitudinal and transverse relaxation occur. Time τ^n is equal to the length of a single 360° pulse. Calculation of cross-relaxation during this sequence by the invariant trajectories method[5] suggests that good cancellation of longitudinal and transverse cross-relaxation can be achieved for resonance offsets of ±0.2 of the field strength. Preliminary experiments with sequence C on OMTKY3 gave results similar to those with pulse sequence B but without the need to calibrate the delay time to compensate for finite pulse length and inhomogeneity effects. Magnetization transfer due to chemical exchange is insensitive to the mixing pulse sequence, since the elementary act of transfer does not depend on the frame of reference. Computer simulation of magnetization motion during the sequence B, neglecting pulse imperfections, has shown that longitudinal magnetization (after 488 cycles) oscillates between 80% and 100% of its full value as a function of resonance offset. This means that, on average, pulse sequence B has inherently 10% smaller sensitivity compared to regular NOESY (or ROESY) sequences. This is seen in the cross section obtained by pulse sequence B (Figure 2C), which exhibits slightly increased noise as compared to that from ordinary NOESY or ROESY sequences (Figures 2A,B).

It is important to note that, in the presence of scalar interactions, the proposed pulse sequences could produce TOCSY (HOHAHA) type cross-peaks. These can be suppressed as in a regular ROESY experiment[17] by a suitable modification of the ROESY mixing periods in sequence A (i.e., by sweeping the spin lock field).

The procedure proposed here allows one to obtain chemical-exchange spectra that are free of interfering cross-relaxation peaks; this capability should increase the reliability of exchange rate measurements in macromolecules. Since chemical exchange can produce effects equivalent to strong spin diffusion, the facile detection of exchange effects should avoid errors in the determination of protein tertiary structure on the basis of information from NOESY spectra. We are currently applying pure exchange spectroscopy to a number of proteins in order to study exchange processes that occur over a wide time scale.

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Nuclear Spin-Spin Coupling via Nonbonded Interactions. 6. F-F Coupling through an Intervening Phenyl Group[1]

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Abstract: Evidence is presented for a novel type of "through-space" nuclear spin-spin coupling involving two fluorine atoms that are intramolecularly crowded against opposite sides of an intervening group X. The first example of this new phenomenon of F-X-F coupling involves the interaction of F-1 and F-8 through the intervening C-9 phenyl group in 1,5,8-trifluoro-9,10-diphenylanthracene (**1**) with a coupling constant of $J_{1,8}$ = 6.4 Hz. The "through-bond" component of this coupling is estimated as 1.1 Hz on the basis that $J_{1,8}$ = 1.1 Hz for 1,5,8-trifluoroanthracene (**2**). The fact that the magnitude of $J_{1,8}$ is significantly larger in **1** than in **2** is attributed to a novel coupling mechanism in **1** involving overlap interactions between the in-plane 2p lone-pair orbitals on the two fluorine atoms and the nearly isoenergetic lowest energy π molecular orbital on the C-9 phenyl group. To rationalize the small value of $J_{1,8}$ = 0.8 Hz for 1,5,8-trifluoroanthraquinone (**3**), it is argued that the in-plane 2p lone-pair orbital on the oxygen atom of the C-9 carbonyl group, which would be the relevant intervening orbital for F-X-F coupling, is much higher in energy than the fluorine in-plane 2p lone-pair orbitals, and this energy mismatch allows only a weak interaction between these two types of orbital.

It is well-known[3] that pairs of fluorine atoms that are intramolecularly crowded against one another can exhibit exceptionally large F-F nuclear spin-spin coupling constants, J_{FF}. Examples include various 1,8-difluoronaphthalenes (J_{FF} = 59-75 Hz)[4] and 4,5-difluorophenanthrenes (J_{FF} = 174 Hz).[5] This phenomenon of "through-space" F-F coupling has been attributed[6] to the generation of a pair of *two*-center molecular orbitals, one bonding and one antibonding, as a consequence of the spatial overlap of two nominally *one*-center 2p lone-pair orbitals as illustrated schematically in Figure 1.

As a corollary of this theory that through-space F-F coupling depends on the overlap of lone-pair orbitals, we predicted earlier that molecules with suitably oriented ^{15}N and ^{19}F atoms should exhibit through-space N-F coupling. The successful experimental verification of that prediction was reported in part 5 of this series.[1a]

We also have used this lone-pair orbital overlap theory to predict the existence of a previously unobserved type of intramolecular spin-spin coupling between fluorine nuclei in which the two fluorine atoms are not crowded directly against one another, but rather are both crowded in a nonbonded way against opposite sides of an intervening group X that bears a p-type lone-pair orbital (or a filled π orbital) oriented such that one lobe of this X orbital overlaps with a 2p lone-pair orbital on one of the fluorine atoms and the other lobe of this X orbital overlaps with a 2p lone-pair orbital on the other fluorine atom. The overlap interactions of these *three* basis atomic orbitals would give rise to a set of *three* molecular orbitals, consisting of one bonding orbital, one nonbonding orbital, and one antibonding orbital. We reasoned that although the six electrons occupying these three molecular orbitals would not provide any net chemical bonding, they should transmit nuclear spin information between the two fluorine nuclei. We now report what we believe is the first example that confirms our theoretical prediction of this novel F-X-F coupling.

Scheme I

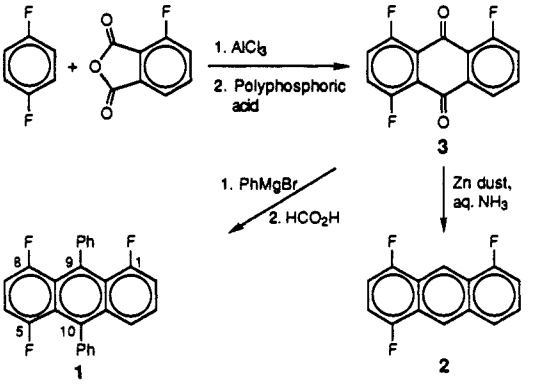

Table I. NMR F-F Coupling Constants (Hz)

compd	$J_{1,8}$	$J_{1,5}$	$J_{5,8}$
1	6.4	1.3	23.0
2	1.1	1.1	22.8
3	0.8	≤0.4	18.1

Results and Discussion

For our first scouting experiment, we chose to compare the coupling between F-1 and F-8 in 1,5,8-trifluoro-9,10-diphenyl-

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