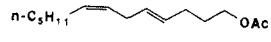
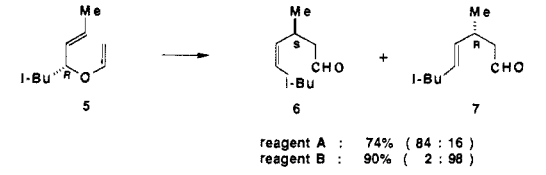
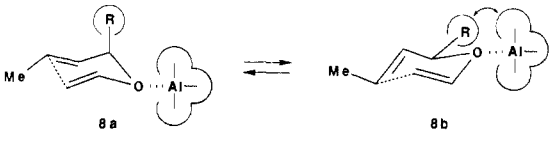
tempted use of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) significantly retarded the rate of the reaction. (5) The rearrangement using the reagent A in toluene somewhat lowered the *Z*-selectivity. A similar propensity for *E*-selectivity was observed with the reagent B in CH_2Cl_2 in lieu of toluene. (6) In case of the substrate **1** (R = Ph), [1,3]-sigmatropic rearrangement took place in competition to the normal [3,3]-Claisen rearrangement (entries 9 and 10). (7) 2-Methyl-1-hepten-3-yl vinyl ether gave the *E*-isomer as a major product even with the reagent A (entry 7). (8) The conjugated *Z*-enyne structural units, which are often present in biologically active natural products,[7] can be readily available by this approach (entry 16). (9) Entries 18 and 19 illustrate the synthetic utility of the present reaction in natural product synthesis. The Claisen product **3**[8] is readily transformed by simple acetylation into (4*E*,7*Z*)-4,7-tridecadienyl acetate (**4**), a component of the sex pheromone of potato tuberworm moth (*Phthorimaea operculella*).[9]



4

Examination of the stereochemical aspect in the rearrangement of the optically active substrate **5** is of special interest in order to elucidate the transition state in the organoaluminum-promoted Claisen rearrangement. Thus, individual treatment of **5** with the reagents A and B under the standard conditions as described above gave the (*S*)-(*Z*)-aldehyde **6** and the (*R*)-(*E*)-aldehyde **7**, re-





spectively as major products with moderate transfer of the chirality of **5** (74–78% chiral transmission).[10,11] Consequently, the observed selectivities are best accounted for by the two possible chairlike transition-state conformations **8a** and **8b** coordinated to the Lewis acidic aluminum reagent.[12] The conformation **8a**, with the R substituent axial, is thought to be highly unfavorable in the Claisen rearrangement and its variants.[1] However, the less likely **8a**, when complexed with the exceptionally bulky organoaluminum reagent, would be favored over **8b** in view of the severe 1,2-steric interaction between R and the aluminum reagent in **8b**, leading to the preferential formation of (*Z*)-alkene. In fact, when the bulkiness of the aluminum reagent is decreased from the reagent A to dimethylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide, the *E*/*Z* selectivity in the rearrangement of the substrate **1** (R = *i*-Bu) is changed dramatically from 7:93 to 71:29, suggesting that the population of the transition state shifts from **8a** to **8b** by decreasing the steric size of aluminum ligands. The origin of the exceedingly high *E*-selectivity with the reagent B, which remains unclear at present, seems to imply the importance of the electronic factor of the 2,6-diphenylphenoxy ligand as well as its steric factor.

Supplementary Material Available: Details for determination of the absolute configurations and the optical purities of **6** and **7** and experimental procedures for the *Z*- and *E*-selective Claisen rearrangements (2 pages). Ordering information is given on any current masthead page.

(7) For example, see: (a) Witkop, B. *Experientia* **1971**, *27*, 1121. (b) Tokuyama, T.; Uenoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. *Helv. Chim. Acta* **1974**, *57*, 2597. (c) Guerreno, A.; Camps, F.; Coll, J.; Riba, M.; Einhorn, J.; Descoins, Ch.; Lallemand, J. Y. *Tetrahedron Lett.* **1981**, *22*, 2013.

(8) We appreciate Dr. S. Tsuboi of Okayama University for providing valuable information on the preparation of the starting allylic vinyl ether.

(9) Previous synthesis of **4**: (a) Roelofs, W. L.; Kochansky, J. P.; Carde, R. T.; Henrick, C. A.; Labovitz, J. N.; Corbin, V. L. *Life Sci.* **1975**, *17*, 699. (b) Voerman, S.; Rothchild, J. *J. Chem. Ecol.* **1978**, *4*, 531. (c) Alexakis, A.; Cahiez, G.; Normant, J. F. *Tetrahedron Lett.* **1978**, 2027. (d) Fujisawa, T.; Sato, T.; Kawashima, M.; Naruse, K.; Tamai, K. *Ibid.* **1982**, *23*, 3583. (e) Nishiyama, H.; Sakuta, K.; Itoh, K. *Ibid.* **1984**, *25*, 223. (f) Vig, O. P.; Sharma, M. L.; Kumari, S.; Rani, V. *Indian J. Chem., Sect. B* **1985**, *24B*, 675. (g) Yadav, J. S.; Reddy, P. S. *Synth. Commun.* **1986**, *16*, 1119. (h) Yadav, J. S.; Kulkarni, A. D.; Reddy, P. S. *Indian J. Chem., Sect. B* **1986**, *25B*, 1220. (i) Chattopadhyay, A.; Mamdapur, V. R.; Chadha, M. S. *Ibid.* **1987**, *26B*, 187.

(10) The ratios of **6** and **7** were determined by capillary GLC after transformation of the Claisen products to the corresponding alcohols and then to the trimethylsilyl ethers.

(11) The absolute configurations of the Claisen products were determined by correlation to optically active citronellal. See Supplementary Material.

(12) The possibility of the boatlike transition-state conformation with the R substituent equatorial, which leads to (*Z*)-alkene, may not be excluded. However, according to the ab initio quantum mechanical calculations the intervention of the boatlike transition structure seems to be unlikely because of the high energy compared to the chairlike transition structure. See: Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314.

Evidence for Dipolar Cross-Correlation from Triple-Quantum-Filtered Two-Dimensional Exchange NMR Spectroscopy

Claudio Dalvit and Geoffrey Bodenhausen*

Institut de Chimie Organique
Université de Lausanne, Rue de la Barre 2
CH-1005 Lausanne, Switzerland
Received June 6, 1988

Two-dimensional nuclear Overhauser effect spectroscopy (NOESY) is now extensively used for structural studies in a large variety of systems.[1-3] The interpretation of NOESY spectra is usually based on Solomon's equations,[4] although these are merely intended to describe the exchange of the two longitudinal Zeeman terms $\langle I_{kz}\rangle$ and $\langle I_{lz}\rangle$ due to cross-relaxation in systems containing only two spins. In a system with three nuclei, however, the relaxation behavior[5-7] can only be fully described by a set of four differential equations, which describe the coupling of the three terms $\langle I_{kz}\rangle$, $\langle I_{lz}\rangle$, $\langle I_{mz}\rangle$, and of longitudinal three-spin order $\langle 4I_{kz}I_{lz}I_{mz}\rangle$. While $\langle I_{kz}\rangle$ and $\langle I_{lz}\rangle$ are coupled through the usual cross-relaxation rate σ_{kl} (which depends only on auto-correlation spectral density functions), $\langle I_{kz}\rangle$ and $\langle 4I_{kz}I_{lz}I_{mz}\rangle$ are coupled by a rate δ_{klkm} that depends on cross-correlation of the dipolar kl and km interactions. If the molecular motion is isotropic, the rate of the conversion from $\langle I_{kz}\rangle$ into $\langle 4I_{kz}I_{lz}I_{mz}\rangle$ is given by[5-8]

$$\delta_{klkm} = c\langle \mathbf{r}_{kl}\rangle^{-3}\langle \mathbf{r}_{km}\rangle^{-3}P_2(\cos\theta_{klkm})\tau_c/(1+\omega_k{}^2\tau_c{}^2) \quad (1)$$

where $c = (^3/_5)(\mu_0/4\pi)^2\gamma^4\hbar^2$ and $P_2(\cos\theta_{klkm}) = {}^1/_2(3\cos^2\theta_{klkm} - 1)$, θ_{klkm} being the angle subtended by the internuclear vectors $\mathbf{r}_{kl}$ and $\mathbf{r}_{km}$. Measuring the initial build-up rate of $\langle 4I_{kz}I_{lz}I_{mz}\rangle$ allows one to determine δ_{klkm}.

The purpose of this communication is to present experimental evidence that longitudinal three-spin order can be separated from the Zeeman terms and that two-dimensional spectroscopy provides a suitable tool for studying cross-correlation.

Three-spin order (or, analogously, octupolar order) has been observed in a selective manner in $^{13}CH_2$ systems by Brondeau et al.,[9] in ^{7}Li ($S = {}^3/_2$) by Jaccard et al.,[10] in methyl groups by

(1) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546-4553.

(2) Macura, S.; Ernst, R. R. *Mol. Phys.* **1980**, *41*, 95-117.

(3) Ernst, R. R.; Bodenhausen, G.; Wokaun, A. *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*; Clarendon Press: Oxford, 1987.

(4) Solomon, I. *Phys. Rev.* **1955**, *99*, 559-565.

(5) Werbelow, L. G.; Grant, D. M. *Adv. Magn. Reson.* **1977**, *9*, 189-299.

(6) Vold, R. L.; Vold, R. R. *Prog. NMR Spectrosc.* **1978**, *12*, 79-133.

(7) Fagerness, P. E.; Grant, D. M.; Kuhlmann, K. F.; Mayne, C. L.; Parry, R. B. *J. Chem. Phys.* **1975**, *63*, 2524-2532.

(8) Böhlen, J. M.; Wimperis, S.; Bodenhausen, G. *J. Magn. Reson.* **1988**, *77*, 589-595.

0002-7863/88/1510-7924$01.50/0

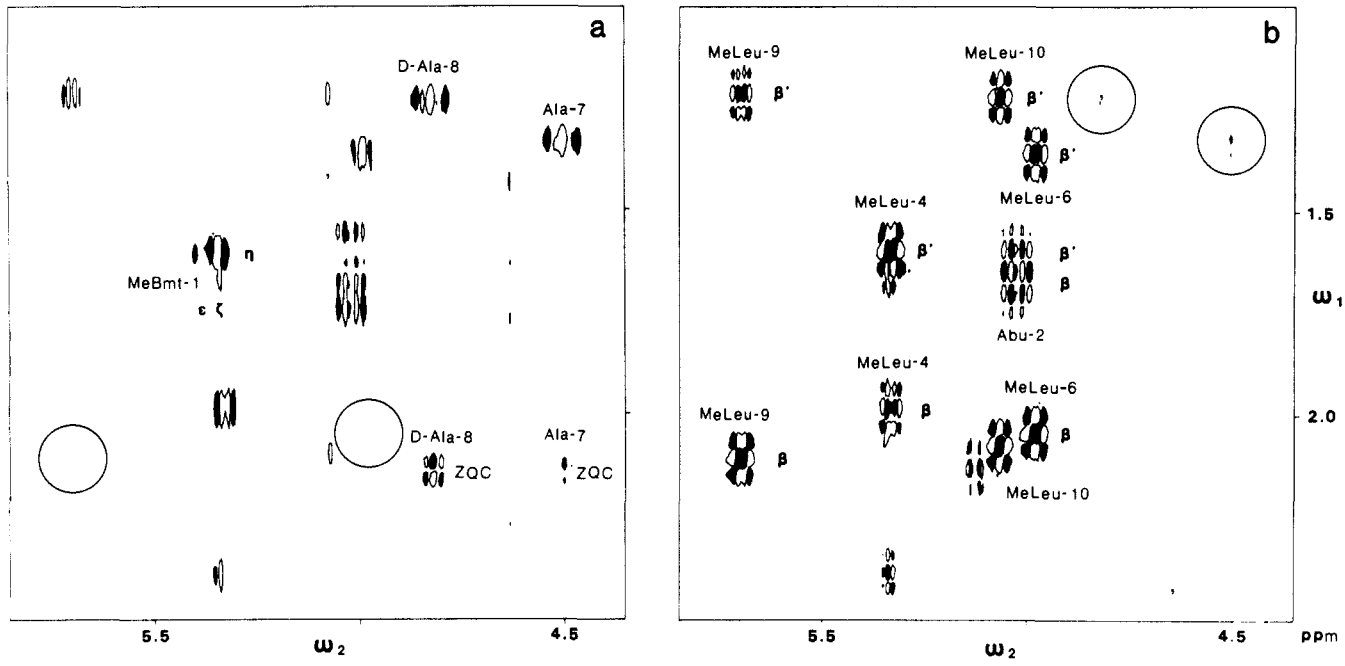


Figure 1. Comparison of (a) triple-quantum-filtered NOESY and (b) triple-quantum-filtered COSY spectra of the α-β region of the cyclic undecapeptide cyclosporine A in $CDCl_3$. The assignments were taken from Kessler et al.[19] Signals due to zero quantum coherences are labeled ZQC. Negative contours have been filled in for clarity. The spectra were recorded with the sequence of eq 2 at 300 K with a Bruker AM 400 spectrometer, with 48 scans for each of the 400 t_1 values.

Müller,[11] and in systems with three inequivalent protons by Böhlen et al.[8] To observe three-spin order, at least two of the three scalar couplings in the three-spin (sub)system must be resolved. Three-spin order cannot be observed in conventional NOESY experiments unless the flip angles of the rf pulse are reduced,[12,13] or unless triple quantum filtration is employed, as suggested by Jaccard et al.[14] and by Bull.[15] The pulse sequence for triple-quantum-filtered two-dimensional exchange spectroscopy (TQF-NOESY) is

$$90° - t_1 - 90° - \tau_m + \chi t_1 - 90° - 90° - t_2 \qquad (2)$$

In practice, the second 90° pulse may be replaced by a composite pulse to ensure that only t_1-modulated Zeeman terms are generated.[16] The mixing time is incremented in concert with the evolution period t_1 in order to displace signals due to zero-quantum coherences in the ω_1 dimension.[17] The usual eight-step phase cycle for the NOESY experiment is combined with a six-step phase cycle for triple quantum filtration (using 60° increments) to yield 48 steps that allow selection of the desirable coherence transfer pathways.[18]

Figure 1a shows the α-β region of the 2D spectrum obtained with this sequence applied to cyclosporine A, an immunosuppressive cyclic undecapeptide.[19] As expected, the multiplets have a doubly antiphase pattern $\{-++-\}$ in the ω_2 domain, and an in-phase multiplet structure in the ω_1 dimension. The comparison with the triple-quantum-filtered COSY spectrum[20] shown in Figure 1b reveals several interesting features. Since all three J couplings are resolved, each of the H^{α}-H^{β}-$H^{\beta'}$ subsystems of the leucine residues leads to three (doubly antiphase) cross-peak multiplets in TQF-COSY (only the α-β and α-β' cross-peaks are shown in Figure 1b). In TQF-NOESY on the other hand, there are in principle three pathways for the creation of longitudinal three-spin order $\langle 4I_z^{\alpha}I_z^{\beta}I_z^{\beta'}\rangle$, which start with the Zeeman orders $\langle I_z^{\alpha}\rangle$, $\langle I_z^{\beta}\rangle$, and $\langle I_z^{\beta'}\rangle$, respectively. In three of the leucines, we observe *only one* of these pathways. For the MeLeu-9 residue, for example, the signal in the top left corner of Figure 1a is due to the transfer from $\langle I_z^{\beta'}\rangle$, i.e., $\delta_{\beta'\alpha\beta'\beta} \neq 0$, while the missing multiplet in the lower left corner of Figure 1a (circled) indicates that $\delta_{\beta\alpha\beta\beta'} \approx 0$. This striking difference in the amplitude of the two pathways may be attributed in part to the fact that $\langle r_{\beta'\alpha}\rangle^{-3}$ is larger than $\langle r_{\beta\alpha}\rangle^{-3}$ (both terms $\delta_{\beta'\alpha\beta'\beta}$ and $\delta_{\beta\alpha\beta\beta'}$ having the same dependence on $\langle r_{\beta\beta'}\rangle^{-3}$). However, these distance factors, taken by themselves, cannot explain an intensity ratio of more than 2 in this system. If the motion is assumed to be isotropic, the observation that $\delta_{\beta\alpha\beta\beta'} \ll \delta_{\beta'\alpha\beta'\beta}$ must largely be due to the fact that $^1/_2(3\cos^2\theta_{\beta\alpha\beta\beta'} - 1)$ is much smaller than $^1/_2(3\cos^2\theta_{\beta'\alpha\beta'\beta} - 1)$, which seems to imply that $\theta_{\beta\alpha\beta\beta'}$ is close to the magic angle of 54.7°. On the other hand, the fact that the transfer $\langle I_z^{\alpha}\rangle \rightarrow \langle 4I_z^{\alpha}I_z^{\beta}I_z^{\beta'}\rangle$ is negligible ($\delta_{\alpha\beta\alpha\beta'} \approx 0$, as evidenced in a part of the spectrum that is not shown here) may be attributed to the fact that $\langle r_{\alpha\beta}\rangle^{-3}\langle r_{\alpha\beta'}\rangle^{-3}$ is small.

Care should be taken if the motion is anisotropic, since the rates δ_{klkm} no longer depend in a simple manner on internuclear angles.[21] The TQF-NOESY spectrum in Figure 1a also shows strong signals due to the AX_3 systems of alanine residues. The signals at $\omega_1 = \Omega_X$ and $\omega_2 = \Omega_A$ (top right in Figure 1a) arise from processes such as $\langle I_z^X\rangle \rightarrow \langle 4I_z^AI_z^XI_z^{X'}\rangle$, which generate three-spin order involving two methyl protons and the α proton. (This should not be confused with third-rank longitudinal order of the three methyl protons[11]). Note that the TQF-COSY spectrum in Figure 1b shows some weak alanine signals (circled), which are due to violations[22-25] of coherence transfer selection rules.[3,20,26]

(9) Brondeau, J.; Canet, D.; Millot, C.; Nery, H.; Werbelow, L. *J. Chem. Phys.* **1985**, *82*, 2212-2216.
(10) Jaccard, G.; Wimperis, S.; Bodenhausen, G. *J. Chem. Phys.* **1986**, *85*, 6282-6293.
(11) Müller, N. *Chem. Phys. Lett.* **1986**, *31*, 218-223.
(12) Oschkinat, H.; Pastore, A.; Bodenhausen, G. *J. Am. Chem. Soc.* **1987**, *109*, 4110-4111.
(13) Oschkinat, H.; Limat, D.; Emsley, L.; Bodenhausen, G. *J. Magn. Reson.* **1988**, in press.
(14) Jaccard, G.; Wimperis, S.; Bodenhausen, G. *Chem. Phys. Lett.* **1987**, *138*, 601-606.
(15) Bull, T. E. *J. Magn. Reson.* **1987**, *72*, 397-413.
(16) Bodenhausen, G.; Wagner, G.; Rance, M.; Sørensen, O. W.; Wüthrich, K.; Ernst, R. R. *J. Magn. Reson.* **1984**, *59*, 542-550.
(17) Macura, S.; Wüthrich, K.; Ernst, R. R. *J. Magn. Reson.* **1982**, *46*, 269-282.
(18) Bodenhausen, G.; Kogler, H.; Ernst, R. R. *J. Magn. Reson.* **1984**, *58*, 370-388.
(19) Kessler, H.; Loosli, H. R.; Oschkinat, H. *Helv. Chim. Acta* **1985**, *68*, 661-681.
(20) Piantini, U.; Sørensen, O. W.; Ernst, R. R. *J. Am. Chem. Soc.* **1982**, *104*, 6800-6801. Shaka, A. J.; Freeman, R. *J. Magn. Reson.* **1983**, *51*, 169-173.
(21) Grant, D. M.; Werbelow, L. G. *J. Magn. Reson.* **1976**, *24*, 369-371.
(22) Müller, N.; Bodenhausen, G.; Wüthrich, K.; Ernst, R. R. *J. Magn. Reson.* **1985**, *65*, 531-534.

Longitudinal three-spin order may be regarded as a *fingerprint* of cross-correlation effects, so that the signals observed in triple-quantum-filtered NOESY spectra provide a direct measure of terms that are usually neglected in routine Overhauser studies. It would be attractive to compare the TQF-NOESY with a normal NOESY spectrum. Unfortunately, the correlation time of cyclosporine in our sample is nearly critical ($\omega_0\tau_c \approx 1.1$), and the cross-relaxation rates σ_{kl} (and hence the NOESY cross-peaks) are very small indeed. It would be necessary to change the experimental conditions (viscosity, temperature) or to obtain cross-relaxation rates in the rotating frame with the CAMELSPIN or ROESY technique,[27,28] but these changes would make a direct comparison more hazardous. Note that the rates δ_{klkm} do *not* vanish for critical correlation times (see eq 1), but that they are negligible for long correlation times, where they cannot compete with the cross-relaxation rates σ_{kl}. Thus in the slow-motion limit relevant to macromolecules, the longitudinal three-spin order terms can be neglected, and N spin systems can safely be described by N-dimensional Solomon equations. This preliminary report suggests that triple-quantum-filtered NOESY experiments may yield valuable information on angles subtended by internuclear vectors in small- and medium-sized molecules. Such measurements hold the promise of broadening the scope of conformational studies.

Acknowledgment. We are indebted to Jean-Marc Böhlen and Stephen Wimperis for theoretical and experimental work which prepared the groundwork for this research and to Dr. Hartmut Oschkinat for valuable advice. We gratefully acknowledge a sample of cyclosporine (Sandimmun) from Dr. D. Römer and Dr. E. Rissi of the Pharma division of Sandoz Ltd, Basle. This research was supported by the Swiss National Science Foundation.

(23) Rance, M.; Wright, P. E. *Chem. Phys. Lett.* **1986**, *124*, 572-575.
(24) Kay, L. E.; Prestegard, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 3829-3835.
(25) Müller, N.; Bodenhausen, G.; Ernst, R. R. *J. Magn. Reson.* **1987**, *75*, 297-334.
(26) Braunschweiler, L.; Bodenhausen, G.; Ernst, R. R. *Mol. Phys.* **1983**, *48*, 535-560.
(27) Bothner-By, A. A.; Stephens, R. L.; Lee, J.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811-813.
(28) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207-213.

Long-Range Heteronuclear Correlation: A Powerful Tool for the NMR Analysis of Medium-Size Proteins

Ad Bax,*,† Steven W. Sparks,‡ and Dennis A. Torchia*,‡

Laboratory of Chemical Physics
National Institute of Diabetes and Digestive and Kidney Diseases
Bone Research Branch, National Institute of Dental Research, National Institutes of Health
Bethesda, Maryland 20892

Received July 18, 1988

The introduction of so-called reverse correlation techniques permits the recording of heteronuclear one-bond $^1H-^{13}C$ and $^1H-^{15}N$ chemical shift correlation spectra of macromolecules at natural abundance.[1-3] Recording of heteronuclear chemical shift correlation spectra via the much smaller two- and three-bond couplings necessarily is much lower in sensitivity because the heteronuclear couplings are comparable to the natural line widths and the homonuclear couplings of the protons. Here, we demonstrate that heteronuclear long range correlations can be observed in a medium-sized protein, provided that isotopic labeling is possible, as it generally is for bacterially overexpressed proteins. The heteronuclear multiple bond correlation (HMBC)[4] spectra provide assignment information as well as qualitative structural information regarding the ϕ, ψ, and χ angles,[5-8] which complement information obtainable from the ^1H spectra.

The HMBC pulse scheme is

$$\begin{array}{lccccc} ^1H: & 90_x\text{-}\Delta\text{-} & & -t_1/2\text{-}180_x\text{-}t_1/2\text{-} & & -\text{Acq.}(t_2) \\ X: & & 90_\phi & & 90_x & \end{array}$$

with the phase cycling $\phi = x, -x$ and Acq. $= x, -x$. The phase ϕ is incremented by 90° for successive t_1 increments (TPPI).[9] To compromise for the effects of the short ^1H transverse relaxation time, the delay, Δ, is set to a value significantly shorter than $1/(2J_{XH})$, typically 40 ms. To optimize sensitivity and resolution, the spectrum is recorded in a mixed-mode absorption in the X chemical shift dimension (F_1) and absolute value mode in the ^1H dimension (F_2).[10] The method has been applied to 1.5 mM samples of a staphylococcal nuclease (S. Nase)/pdTp/calcium complex (18 kD) in D_2O, $p^2H = 7.4$, 100 mM NaCl. Sample I has all Leu, Ile, and His residues labeled with $^{15}N\alpha$; sample II has all Thr residues labeled with ^{13}C in the carbonyl position.

The $^1H-^{15}N$ and $^1H-^{13}C$ HMBC spectra, obtained for the two samples, are shown in Figure 1. The assignments indicated are based on a large number of isotopic labeling and double labeling experiments[11] and will be published elsewhere. As can be seen in Figure 1, both two-bond and three-bond correlations are observed, but either is present for all labeled residues. The intensity of the observed correlation depends on the size of the long range coupling and on the width of the ^1H multiplet. Because of short transverse relaxation times and because of homonuclear J modulation during the relatively long delay, Δ, and during the t_1 and t_2 periods, the intensity of the typically unresolved ^1H multiplet rapidly decreases at a rate proportional to the reciprocal of its width (which approximately equals the sum of all homonuclear ^1H couplings). Nevertheless, three-bond couplings involving the $C^\alpha H$ proton that are expected to be larger than about 5 Hz (based on the X-ray crystal structure and suitable Karplus equations[5]) invariably give rise to observable correlations; correlations are not observed when the couplings are smaller than about 2.5 Hz.

Thus, it is seen in Figure 1A that for all residues in α-helical regions of the protein[12] a correlation is observed between $C^\alpha H(i)$ and $^{15}N(i+1)$ ($\psi \approx -50°$; $^3J_{NH} \approx 6$ Hz). No such correlation is observed for any of the β-strand residues ($\psi \approx 130°$; $^3J_{NH} <$ 1.5 Hz). The short transverse relaxation times of nonmobile C^β methylene protons (≈15 ms for S. Nase) is the likely reason why very few intraresidue $C^\beta H-^{15}N$ correlations are observed. Two intense correlations observed for the $C^\beta H$ protons of His-8 (complemented by two intense $C^\alpha H-C^\beta H$ correlations in the COSY and HOHAHA spectra, data not shown) suggest that the side chain of this residue has significant conformational flexibility. Similarly, the mobile residues Val-5′, Ala-1, and Ala-145 show intense correlations despite low levels of ^{15}N cross-labeling (Val 5%, Ala 1.5%).

$^1H-^{13}C_i$ correlations (Figure 1B) contain information about the ϕ and χ angles, and, as previously demonstrated for peptides,[6,8,13] they can also provide sequential connectivity information

† Laboratory of Chemical Physics.
‡ Bone Research Branch.

(1) Wagner, G.; Bruewihler, D. *Biochemistry* **1986**, *25*, 5839.
(2) Sklenar, V.; Bax, A. *J. Magn. Reson.* **1987**, *71*, 379.
(3) Live, D. H.; Davis, D. G.; Agosta, W. C.; Cowburn, D. *J. Am. Chem. Soc.* **1984**, *106*, 6104.
(4) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
(5) Bystrov, V. F. *Prog. Nucl. Magn. Reson. Spectrosc.* **1976**, *10*, 41.
(6) Bystrov, V. F.; Okhanov, V. V.; Arseniev, A. S.; Adanasiev, V. A.; Gurevich, A. Z. *Biorg. Khim.* **1980**, *6*, 383. Bystrov, V. F.; Okhanov, V. V.; Miroshnikov, A. I.; Ovchinikov, Y. A. *FEBS Lett.* **1980**, *119*, 113.
(7) Cowburn, D.; Live, D. H.; Fischman, A. J.; Agosta, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 7435.
(8) Kessler, H.; Griesinger, C.; Wagner, K. *J. Am. Chem. Soc.* **1987**, *109*, 6927.
(9) Marion, D.; Wuethrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 967.
(10) Bax, A.; Marion, D. *J. Magn. Reson.* **1988**, *78*, 186. Note that the F_1 phase correction needed is $2\pi T$ per Hz, not $2\pi/T$ as stated in this paper.
(11) Griffey, R. H.; Redfield, A. G. *Quart. Rev. Biophys.* **1987**, *19*, 51.
(12) Tucker, P. W.; Hazen, E. E.; Cotton, F. A. *Mol. Cell. Biol.* **1979**, *23*, 67.
(13) Wynants, C.; Hallenga, K.; van Binst, G.; Michel, A.; Zanen, J. *J. Magn. Reson.* **1984**, *57*, 93.

0002-7863/88/1510-7926$01.50/0 Published 1988 by the American Chemical Society