and *not* the hydrogen-bonded *endo*-2'-hydroxyaverufin (**2b**) as previously assumed.

If a nidurufin-type intermediate is indeed involved in the averufin to versicolorin A transformation, it seems likely that this intermediate is the *exo*-alcohol nidurufin (**2a**) and not the unknown C-2' endo isomer epinidurufin (**2b**), since only **2a** has the favorable stereochemistry for an AR_13-promoted rearrangement.

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Registry No. 2a, 28458-23-3; **5**, 518-83-2; **6**, 92762-95-3; **6**-ol, 92762-96-4; **6** (chloro derivative), 92762-97-5; **7**, 92762-98-6; **8**, 92762-99-7; **9**, 92763-00-3; **9a**, 92763-01-4; **10**, 92763-02-5; **11**, 92842-94-9; **5** (methoxymethyl ether), 64517-18-6; **5** (allyl ether), 92763-03-6.

Spin Multiplet Enhancement in Two-Dimensional Correlated NMR Spectroscopy

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Two-dimensional (2D) homonuclear correlated spectroscopy[1-4] is probably the most widely used 2D NMR experiment to date. It has proven to be a convenient and powerful method for tracing the pattern of homonuclear couplings in molecules with a molecular weight of up to 10000 daltons. However, it appears in practice that the intensity of a cross multiplet, indicating spin coupling, is not directly related to the magnitude of the homonuclear coupling involved. Sometimes protons that have a large scalar interaction show vanishing intensity for the cross multiplet. We propose a method for enhancing selectively the intensity of certain cross peaks of interest and for improving the sensitivity of the experiment.

From the recently introduced operator formalism approach,[5-7] it is easily found that the amount of magnetization transfer, R_1, from nucleus A to nucleus X in the COSY experiment has the proportionality

$$R_1(t_1) = \sin(\pi J_{AX} t_1) \prod_k \cos(\pi J_{Ak} t_1) \quad (1a)$$

where k denotes the nuclei other than X to which A is coupled, and t_1 is the duration of the evolution period. Just after the mixing pulse, magnetization transferred from A to X is in antiphase with respect to spin A[2,5] and in phase with respect to other spins, n, to which X is coupled. The detected X spin magnetization has the t_2 (detection time) dependence:

$$R_2(t_2) = \sin(\pi J_{AX} t_2) \prod_n \cos(\pi J_{Xn} t_2) \quad (1b)$$

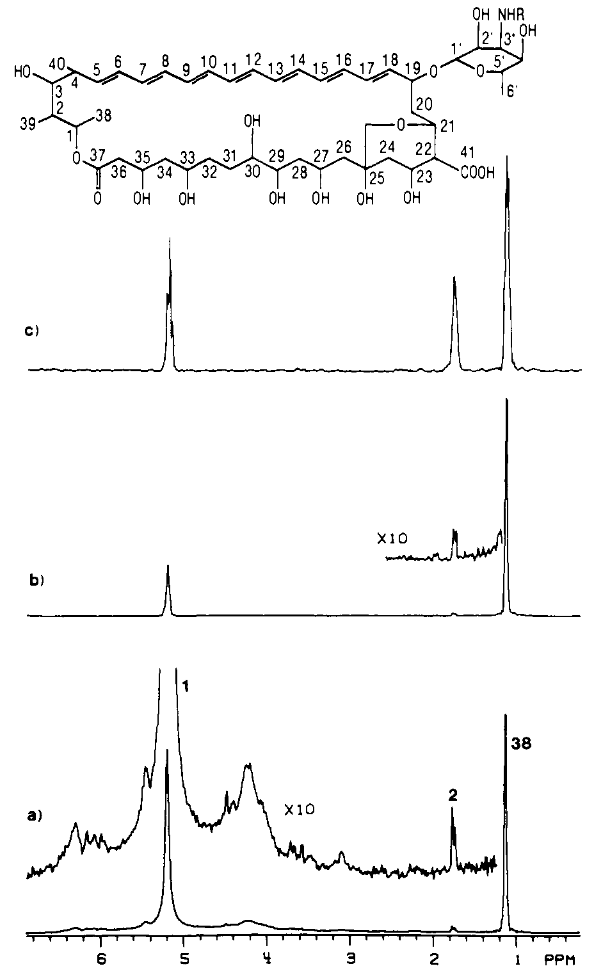

Figure 1. Cross sections parallel to the F_1 axis through the 2D COSY spectra of a sample of amphotericin B, recorded at 500 MHz. The cross sections are taken at the F_2 frequency of proton H1. (a) Cross section if no digital filtering is used, (b) cross section if a single sine bell is used in both dimensions, and (c) the cross section obtained if the optimized filter of eq 3 is used in order to emphasize the H1-H2 cross peak.

If the experiment is performed with phase modulation and n-type (coherence-transfer echo) selection,[8] the detected X spin magnetization, originating from A, is then given by

$$s_{AX}(t_1,t_2) = M_{0A}[R_1(t_1)R_2(t_2)\exp(-t_1/T_{2A})\exp(-t_2/T_{2X})] \times \exp(-i\Omega_A t_1)\exp(i\Omega_X t_2) \quad (2)$$

where M_{0A} denotes the longitudinal A spin magnetization just before the first pulse of the COSY experiment, and T_{2A} and T_{2X} are the transverse relaxation times of A and X. From the terms within the square brackets in eq 2, it is seen that the magnetization transfer from A to X does not only depend on the magnitude of J_{AX} but also on the couplings between A and spins k and between X and spins n. Optimal signal to noise for the AX cross multiplet will be obtained for matched filtering, i.e., by multipyling the time domain signal with the function within the square brackets in eq 2. This function is specific for magnetization transferred from A to X and will be nonmatched filtering for other magnetization components. Consequently, diagonal components will be strongly attenuated by such a function, as are other cross peaks that show a different multiplet structure. It is clear from eq 2 that cross peaks between A and X will be hard to observe, if both A and X are coupled to a large number of other spins. However, by the use of a filtering function matched for that particular transfer, all other magnetization components are attenuated relative to the magnetization that contributes to the AX cross peak.

(1) Jeener, J. Ampere International Summer School, Basko Polje, Yugoslavia, 1971.
(2) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229.
(3) Bax, A.; Freeman, R.; Morris, G. A. *J. Magn. Reson.* **1982**, *42*, 164.
(4) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542.
(5) Sorensen, O. W.; Eich, G. W.; Levitt, M. H.; Bodenhausen, G.; Ernst, R. R. *Progr. Nucl. Magn. Reson. Spectrosc.* **1983**, *16*, 163.
(6) Van de Ven, F. J. M.; Hilbers, C. W. *J. Magn. Reson.* **1983**, *54*, 512.
(7) Packer, K. J.; Wright, K. M. *Mol. Phys.* **1983**, *50*, 797.
(8) Nagayama, K.; Kumar, A.; Wüthrich, K.; Ernst, R. R. *J. Magn. Reson.* **1980**, *40*, 321.

In practice, of course, multiplets of protons A and X have usually not been identified in the regular one-dimensional spectrum, and exact values for the spin couplings involved are unknown. However, an approximate guess for those values is sufficient for fruitful use of the "mulitplet-selective filter", especially since acquisition times, AT, in the t_1 and t_2 dimensions usually have a duration of only one to several hundred milliseconds.

As an example, Figure 1 compares absolute value mode cross sections taken parallel to the F_1 axis at the F_2 frequency of proton H1 through three COSY spectra, all obtained from the same set of acquired data, for a sample of amphotericin B in Me_2SO-d_6. Figure 1a shows the cross section obtained if no digital filtering is used. The diagonal peak shows a broad base due to the absolute value mode and the in-phase nature of the unresolved multiplet components. The cross peak with Me38 is strong, but the cross peak with proton H2 has very low intensity. The noise in this trace is partly so-called t_1 noise[9,10] and arises from instabilities in the spectrometer system which cause some of the signal energy of the intense peaks (H1 and Me38) to be distributed over the entire trace. Figure 1b shows the trace that is obtained if the commonly used sine-bell function is applied in both dimensions. The line shape is improved and the diagonal peak (H1) is attenuated compared with Figure 1a, but the H1–Me38 cross peak is still a factor of about 60 stronger than the H1–H2 cross peak. Figure 1c shows the cross section that is obtained if the multiplet selection procedure, described earlier, is applied in order to emphasize the H1–H2 cross peak. The signal-to-noise ratio for the H1–H2 cross peak has improved dramatically, mainly because of the matched filtering in both dimensions but also because the intense resonances in this F_1 section, which are the major contributors to t_1 noise, are attenuated. Note that the use of the multiplet-selective filter introduces a broadening of the multiplet structure in both frequency dimensions.

The H1–H2 cross peak has been enhanced to within about a factor of 2 relative to the H1–Me38 cross peak. Both H1 and H2 are coupled to methyl groups, and this coupling is estimated to be 7 Hz. The H1–H2 coupling is unknown but is estimated at 5 Hz. The H2–H3 coupling is unknown and is not incorporated in the filtering function. The total filtering function, $G(t)$, used in both dimensions for a duration of the acquisition time, AT, is given by

$$G(t) = \cos(7\pi t)^3 \sin(5\pi t) \sin(\pi t/\mathrm{AT}) \quad (3)$$

The last factor of this function denotes a sine bell, added to the optimized filter in order to avoid truncation of the time domain data at the end of the FID.

We have shown that the relative intensity and sensitivity of cross peaks in homonuclear correlated spectra can be increased dramatically by use of digital filtering procedures optimized for this purpose. This approach is particularly important for the common case where small impurities are present in the sample, and low contour levels in a regular COSY spectrum show a jumble of corresponding cross peaks. Also, by trying a number of different filtering functions one is able to distinguish between cross peaks due to relatively large couplings and small long-range couplings. The method is also applicable in heteronuclear[11] and homonuclear relayed coherence transfer spectroscopy[12,13] and in proton double-quantum spectroscopy.[14]

In view of improvements in computer technology and incorporation of array processors in commercial spectrometers, we expect that the extra data processing time, needed for reprocessing the same set of time domain data several times, will not be a major factor in the near future.

(9) Nagayama, K.; Bachman, P.; Wüthrich, K.; Ernst, R. R. *J. Magn. Reson.* **1978**, *31*, 133.
(10) Mehlkopf, A. F.; Korbee, D.; Tiggelman, T. A.; Freeman, R. *J. Magn. Reson.* **1984**, *58*, 315.
(11) Bolton, P. H. *J. Magn. Reson.* **1982**, *48*, 336.
(12) Eich, G.; Bodenhausen, G.; Ernst, R. R. *J. Am. Chem. Soc.* **1982**, *104*, 3732.
(13) Bax, A.; Drobny, G. *J. Magn. Reson.*, in press.
(14) Mareci, T. H.; Freeman, R. *J. Magn. Reson.* **1983**, *51*, 531.

Fluoride Ion Induced Rearrangements of Chloromethyl-Substituted Silanes: Carbanionic Character of Groups Undergoing Migration

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We have discovered that chloromethyl-substituted silanes undergo alkyl- and aryl-group rearrangement induced by fluoride ion solubilized by 18-crown-6. This migration is largely controlled by the ability of the migrating group to bear the negative charge which develops in the transition state.

Considerable recent activity has focused on the degree of anionic character associated with groups cleaved from silicon by nucleophiles, particularly in cases where the pK_a values of the groups undergoing cleavage are less than 37.[1] Such reactions are induced both by basic and fluoride ion catalysis, generally from trimethylsilyl-substituted derivatives.[1] A variety of correlations between substituent and acidity constants and rates or relative rates of cleavage has made it clear in such reactions that the cleaved carbon fragment has substantial carbanionic character.[1,2]

Quite recently we have measured the gas-phase acidities of some weakly acidic hydrocarbons by reaction of hydroxide ion with several trimethylsilyl-substituted alkanes.[3] Indeed, we have found a remarkable correlation between the gas-phase acidities of RH (ΔH°_{acid}) and the product ratio (**1**/**2**) resulting from competitive cleavage producing CH_3H and RH in eq 1.

$$(CH_3)_3SiR \xrightarrow{OH^-} \underset{\mathbf{1}}{(CH_3)_3SiO^-} + R\text{–}H$$
$$\rightarrow \underset{\mathbf{2}}{(CH_3)_2RSiO^-} + CH_3\text{–}H \quad (1)$$

We report here on some solution-phase work involving the rearrangement of alkyl and aryl groups. This work is particularly important because it occurs in condensed phase with the migration of groups that are weakly acidic. Thus, it partially bridges a gap between the studies just discussed. We have found that (chloromethyl)trimethylsilane reacts with potassium or cesium fluoride in the presence of 18-crown-6 in aromatic hydrocarbon solvents to give exclusively dimethylethylfluorosilane (eq 2). Although

$$\underset{\mathbf{3}}{(CH_3)_3SiCH_2Cl} \xrightarrow[\text{toluene}]{\text{18-crown-6, KF or CsF}} (CH_3)_2(CH_3CH_2)SiF \quad (2)$$

related rearrangements of chloromethyl-substituted silanes under acidic conditions (e.g., aluminum chloride catalysis) have been reported and studied in detail,[4] only a few examples of base-induced reaction of chloromethyl-substituted silanes are known and these rarely involve the migration of a simple alkyl group.[5] Nevertheless, two reports of alkyl migration are relevant to this

(1) (a) Seconi, G.; Taddei, M.; Eaborn, C. *J. Chem. Soc., Perkin Trans. 2* **1982**, 643–646. (b) Eaborn, C.; Stamper, J. G.; Seconi, G. *J. Organomet. Chem.* **1981**, *204*, 27–45. (c) Effenberger, F.; Spiegler, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 265–266. (d) Ricci, A.; Degl'Innocenti, A.; Fiorenza, M.; Taddei, M.; Spartera, M.; Walton, D. R. M. *Tetrahedron Lett.* **1982**, *23*, 577–578.
(2) (a) Eaborn, C.; Walton, D. R. M.; Seconi, G. *J. Chem. Soc., Chem. Commun.* **1975**, 937–938. (b) Fischer, A.; Morgan, M. W.; Eaborn, C. *J. Organomet. Chem.* **1977**, *136*, 323–332. (c) Bott, R. W.; Eaborn, C.; Swaddle, T. W. *J. Chem. Soc.* **1963**, 2342–2347.
(3) DePuy, C. H.; Bierbaum, V. M.; Damrauer, R. *J. Am. Chem. Soc.* **1984**, *106*, 4051–4053.
(4) (a) Bott, R. W.; Eaborn, C.; Rushton, B. M. *J. Organomet. Chem.* **1965**, *3*, 455–463. (b) Kumada, M.; Ishikawa, M. *J. Organomet. Chem.* **1964**, *1*, 411–419.
(5) Corey, J. Y.; Corey, E. R.; Chang, V. H. T.; Hauser, M. A.; Leiber, M. A.; Reinsel, T. E.; Riva, M. E. *Organometallics* **1984**, *3*, 1051–1060. This paper reviews in detail the literature of base-induced rearrangements of chloromethyl-substituted silanes including both fluoride- and alkoxide-induced rearrangements.