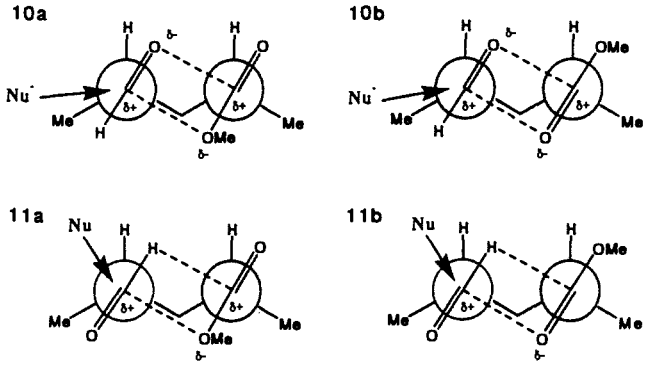
also gave the anti-Cram products with high diastereoselectivity (95/5).

The anti-Cram selectivity of **1** can be accounted for by the model **10**. Both δ^+ and δ^- terminals of the aldehyde interact with the δ^- and δ^+ terminals of the ester. It is not clear at present which is more stable, **10a** or **10b**. The nucleophile attacks as indicated



by an arrow, giving the anti-Cram products. The conformations **11a,b** leading to the Cram products have only one interaction between $C^{\delta+}$ and $O^{\delta-}$ and thus are less stable than **10**. It is now clear that **1** is a conformationally rigid acyclic molecule. The driving force for the conformational lock is presumably an electrostatic interaction between two carbonyl groups[9] in addition to the presence of the properly oriented Me groups. A conceptual extension of the present finding has aroused our interest in searching for other related acyclic rigid systems, and those works will be reported shortly.

Supplementary Material Available: ^1H NMR spectra of **1** and **2**, their NOE spectra, ^{13}C NMR spectra in the presence of $SnCl_4$, and product identification (**6–9**) (8 pages). Ordering information is given on any current masthead page.

(9) Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1988**, *110*, 6794. Any information on the conformation around the aldehyde function cannot be obtained by the NMR experiments. MM2 calculations indicated that **10b** is the most stable conformation. This will be published in due course.

3D Heteronuclear Nuclear Magnetic Resonance Techniques for Carbon-13 in Natural Abundance

H. Kessler* and P. Schmieder

Organisch-Chemisches Institut, TU München
Lichtenbergstrasse 4, D-8046 Garching, FRG

H. Oschkinat

Max-Planck-Institut für Biochemie
Am Klopferspitz, D-8033 Martinsried, FRG

Received June 4, 1990

NMR spectroscopy is now established as a standard technique for structure determination in solution.[1,2] For the investigation of larger molecules, methods to increase the resolution are required to cope with the increasing complexity of the spectra. It has been shown that heteronuclear 3D NMR can be effectively used to simplify NMR spectra of unlabeled molecules.[3] However, for proteins, isotopic enrichment is mostly[4] used for heteronuclear

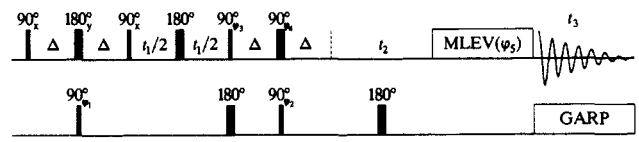


Figure 1. Pulse sequence of the 3D-HQQC-TOCSY spectrum. The delays Δ are set to $(1/2^1J_{CH})$. The following phase cycle is applied: φ_1 = 0, 180, 0, 180; φ_2 = 0, 0, 180, 180; φ_3 = 4 × 0, 4 × 60, 4 × 120, 4 × 180, 4 × 240, 4 × 300; φ_4 = 4 × 90, 4 × 150, 4 × 210, 4 × 270, 4 × 330, 4 × 30; φ_5 = 4 × 270, 4 × 150, 4 × 30; rec = 180, 0, 0, 180, 60, 240, 240, 60, 300, 120, 120, 300. In the spectrum recorded here a BIRD pulse[12] prior to acquisition was applied to suppress protons not bound to ^{13}C and to allow for rapid pulsing.[13]

2D[5] and 3D[6] techniques. The most sensitive way to record heteronuclear correlations is through application of the so-called "inverse" techniques,[7] since the nucleus with the highest gyromagnetic ratio (^1H) is used for excitation and detection. However, one drawback of these techniques is that the spectral resolution of the indirectly detected dimensions is limited by the number of increments in the evolution time (t_1 for 2D, t_1 and t_2 for 3D). No electronic filtering is possible, and it is difficult to find a suitable compromise between resolution and measuring time, especially with carbon as the hetereonucleus, since the resonances are spread over a large spectral range. One apprach to tackling this problem is folding in the carbon dimension[8] which, however, requires a sufficiently large spectral width in the virtual proton dimension. Alternatively the use of soft pulses may allow restriction of the spectral width to a large extent at the expense of experimental simplicity and a nonrectangular excitation profile. In this paper we present a technique for simultaneous frequency selection in F_1 and F_2 allowing the recording of well-resolved heteronuclear 3D NMR spectra with samples in natural abundance in reasonable measuring times (16 h to 2 days).

The techniques we describe overcome the above-mentioned problem by multiplicity filtering (selection and/or editing) of CH_3 or CH_2 via DEPT-like[9] excitation and selection of heteronuclear multiple quantum coherences.[3c,10] Since the ranges of carbon resonances of the multiplicities CH_2 and CH_3 are normally only 40 and 20 ppm, respectively, this results in a drastic reduction of the spectral width without having to use selective pulses. The same holds for the spectral range of the protons bound to these carbons.

The sequences described here (Figure 1) share a common pulse sequence but utilize two different phase cycles to yield two different effects: (a) selection of CH_3 and (b) selection of CH_2.

In the first delay (Δ), heteronuclear antiphase magnetization is created and is converted to heteronuclear double quantum coherence by a 90° carbon pulse. In the second delay, heteronuclear coupling evolves again, but now depending on the multiplicity of the carbon. The following 90° proton pulse creates heteronuclear triple or quadruple quantum coherence and leaves the double quantum coherence unaffected. During t_1 these coherences are then labeled with the chemical shift of the carbon and through an appropriate multiquantum selection the different

(1) Wüthrich, K. *NMR of proteins and Nucleic Acids*; Wiley: New York, 1986.
(2) Kessler, H.; Gehrke, M.; Griesinger, C. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 490–536.
(3) (a) Fesik, S. W.; Gampe, R. T., Jr.; Zuiderweg, E. R. P. *J. Am. Chem. Soc.* **1989**, *111*, 770–772. (b) Griesinger, C.; Sørensen, O. W.; Ernst, R. R. *J. Magn. Reson.* **1989**, *84*, 14–63. (c) Schmieder, P.; Kessler, H.; Oschkinat, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 546–548.
(4) (a) Wagner, G.; Brühwiler, D. *Biochemistry* **1986**, *25*, 5839–5843. (b) Kessler, H.; Schmieder, P.; Bermel, W. *Biopolymers*, in press.
(5) (a) Stockman, B. J.; Reily, M. D.; Westler, W. M.; Ulrich, E. L.; Markley, J. L. *Biochemistry* **1989**, *28*, 230–236. (b) Shon, K.; Opella, S. J. *J. Magn. Reson.* **1989**, *82*, 193–197. (c) Gronenborn, A. M.; Wingfield, P. T.; Clore, G. M. *Biochemistry* **1989**, *28*, 5081–5089.
(6) (a) Fesik, S. W.; Zuiderweg, E. R. P. *J. Magn. Reson.* **1988**, *78*, 588–593. (b) Kay, L. E.; Marion, D.; Bax, A. *J. Magn. Reson.* **1989**, *84*, 72–84.
(7) (a) Maudsley, A. A.; Ernst, R. R. *Chem. Phys. Lett.* **1977**, *50*, 368–372. (b) Müller, L. *J. Am. Chem. Soc.* **1979**, *101*, 4481–4484. (c) Bodenhausen, G.; Ruben, D. J. *Chem. Phys. Lett.* **1980**, *69*, 185–189. (d) Bax, A.; Griffey, R. H.; Hawkins, B. L. *J. Magn. Reson.* **1983**, *55*, 301–315.
(8) Ikura, M.; Kay, L. E.; Tschudin, R.; Bax, A. *J. Magn. Reson.* **1990**, *86*, 204–209.
(9) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323–327.
(10) (a) Kay, L. E.; Bax, A. *J. Magn. Reson.* **1989**, *84*, 598–603. (b) Kessler, H.; Schmieder, P.; Kurz, M. *J. Magn. Reson.* **1989**, *85*, 400–405. (c) Schmidt, J. M.; Rüterjans, H. *J. Am. Chem. Soc.* **1990**, *112*, 1279–1280. (d) Kessler, H.; Schmieder, P.; Köck, M.; Reggelin, M. *J. Magn. Reson.*, in press. (e) Kessler, H.; Schmieder, P. *Biopolymers*, in press.

0002-7863/90/1512-8599$02.50/0

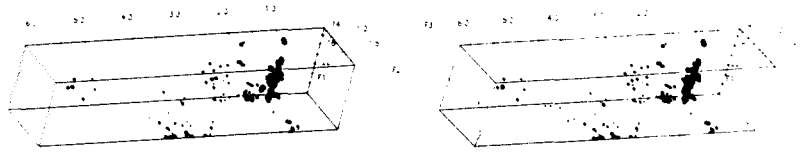


Figure 2. Stereoscopic picture of the 3D-HQQC-TOCSY spectrum of thio-(1)-cyclosporin A, processed on a Convex instrument with own software[14] and displayed on an Evans and Sutherland PS330 graphic station. The spectrum was recorded with a sample of 14 mmol/L. The crowded region on the right shows the resonances of the methyl groups, the region in the middle shows the relay peaks to the H^{β} and H^{γ} peaks, and the region on the left shows the relay peaks to the H^{α} peaks. The spectrum was recorded with 48 scans for each fid (spectral width 6250 Hz in F_3), 96 increments in t_1 (spectral width 1710 Hz), and 78 increments in t_2 (spectral width 1250 Hz), leading to high resolution and a relatively long total measuring time of 44 h. The mixing time of the MLEV-17 mixing was 75 ms. The spectrum was recorded as F_1/F_3 slices on a Bruker AMX 500 instrument. No dummy scans had to be applied; the sample was not spun.

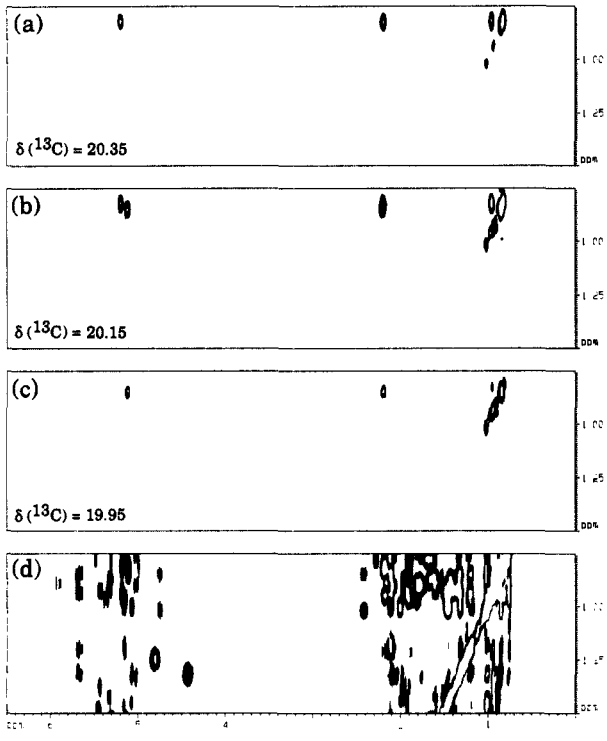


Figure 3. Parts a-c show three adjacent F_2/F_3 slices through the 3D-HQQC-TOCSY spectrum at the carbon resonances shown in the picture. The peaks result from the spin systems of MeVal-11 in both conformers of thio-(1)-cyclosporin A. Part d shows the same region of a 2D-TOCSY spectrum. The increased resolution in the 3D spectrum is clearly visible, and an assignment is straightforward, although the carbon shift of both methyl groups present in these three slices differs only by 0.14 ppm (20 Hz). The slices have been processed on a Bruker X32 data station with standard software and some additional sorting programs written in C.

multiplicities can be differentiated: Heteronuclear quadruple quantum coherence (HQQC) selects CH_3 (a), and triple quantum coherence (HTQC), CH_2 (b). A second evolution period and another transfer step lead to a 3D sequence.

We show here the application of 3D-HQQC-TOCSY (case a, selection of CH_3) to thio-(1)-cyclosporin A.[11] This molecule exists in two conformations (58:42) in $CDCl_3$ and thus exhibits resonances from 48 CH_3 groups, 14 of which are NCH_3 and show no relevant homonuclear couplings. A 2D HMQC-TOCSY was not sufficient to remove all ambiguities in the assignment of these resonances. A stereoscopic picture of the 3D-HQQC-TOCSY spectrum is shown in Figure 2. Three 2D slices from this spectrum are shown in Figure 3 and compared to their 2D analogue to demonstrate the increased resolution. It is obvious from Figure 3 that resonances with carbon chemical shift differences of only 0.14 ppm can be resolved and the proton spectrum elucidated. This would be extremely difficult by conventional methods, especially as the H^{β} resonances at 2.15 ppm are overlapped. Almost all other resonances are better separated in CH correlation (equivalent to the F_1/F_2 projection of the 3D spectrum), hence allowing a total assignment of even such a crowded spectrum. A similar result has been obtained for CH_2 groups (case b, spectrum presented elsewhere[10e]).

In conclusion, we have presented techniques that can be routinely applied to elucidate homo- and heteronuclear spin systems. The potential of these techniques lies in the simultaneous assignment of proton and carbon resonances in crowded spectra by exploiting the high resolution of carbon resonances for the identification of the total proton spin system. It should also be noted that the exclusive excitation of methyl groups works as a filter for a restricted number of amino acids. A special advantage of the proposed technique is that it can be applied to carbon in natural abundance. It is often not possible or extremely cumbersome to label a natural product whose structure elucidation is of interest. In such cases these techniques will find application.

Acknowledgment. Financial support of the Deutsche Foschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. H.O. thanks the Bundesministerium für Forschung und Technologie (Grant 321/4003/0318909A).

(11) The sulfur analogue of cyclosporin A was obtained from Prof. D. Seebach (ETH Zürich) and is currently being investigated in our laboratory. It has been shown by NMR that the sulfur is on the amino acid in position 1 (Mebmt), thus we like to call it thio-(1)-cyclosporin A.

(12) Garbow, J. R.; Weitekamp, D. P.; Pines, A. *Chem. Phys. Lett.* **1982**, *93*, 504-509.
(13) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565-569.
(14) Oschkinat, H.; Cieslar, C.; Holak, T. A.; Clore, G. M.; Gronenborn, A. M. *J. Magn. Reson.* **1989**, *83*, 450-472.

Synthesis and Reactions of a New Rhenium(V) Oxo Hydrido Complex. Transfer of Both Oxygen and Hydrogen to Carbon Monoxide

Youhyuk Kim, Judith Gallucci, and Andrew Wojcicki*

Department of Chemistry, The Ohio State University Columbus, Ohio 43210

Received June 18, 1990

In recent years there has been a remarkable surge of research activity concerned with transition-metal oxo complexes.[1] These complexes find important applications in organic synthesis and in heterogeneous and biochemical catalysis. The introduction of hydride ligands into metal oxo complexes is further expected to provide model systems for investigations of metal-catalyzed reactions of such species as H_2O, O_2, peroxides, and superoxides with various organic and inorganic substrates. In view of the potential applications of metal oxo hydrido complexes, it is surprising that only three examples, viz., $(\eta^5\text{-}C_5Me_5)_2Ta(O)H$[2] and

(1) Books and reviews: (a) Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; Wiley: New York, 1988. (b) Kochi, J. K.; Sheldon, R. A. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (c) Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401. (d) Schröder, M. *Chem. Rev.* **1980**, *80*, 187. (e) Bottomley, F.; Sutin, L. *Adv. Organomet. Chem.* **1988**, *28*, 339. (f) Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1297.
(2) van Asselt, A.; Burger, B. J.; Gibson, V. C.; Bercaw, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 5347.

0002-7863/90/1512-8600$02.50/0