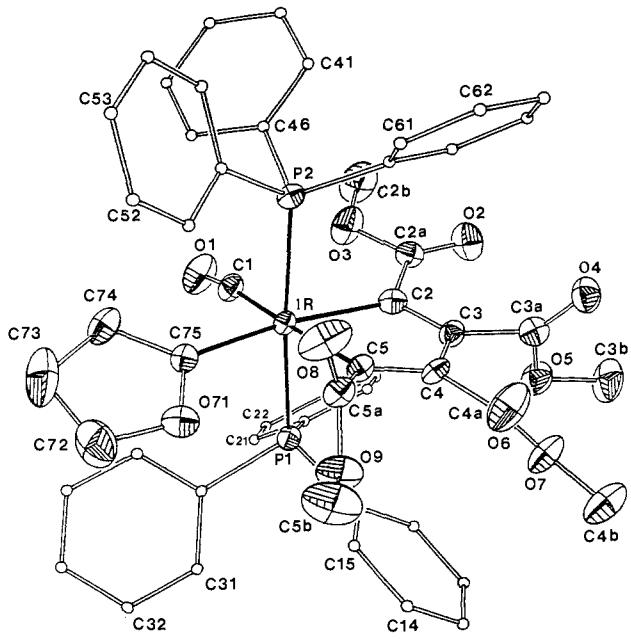

Figure 1. Molecular structure and labeling scheme for **2**: Ir–P(1), 2.445 (2); Ir–P(2), 2.403 (2); Ir–C(1), 1.925 (8); Ir–C(2), 2.108 (7); Ir–C(5), 2.101 (7); Ir–C(75), 2.025 (7); C(2)–C(3), 1.33 (1); C(3)–C(4), 1.48 (1); C(4)–C(5), 1.33 (1) Å; P(1)–Ir–P(2), 172.6 (1); P(1)–Ir–C(1), 84.7 (2); P(1)–Ir–C(2), 85.0 (2); P(1)–Ir–C(5), 91.5 (2); P(1)–Ir–C(75), 91.6 (2); P(2)–Ir–C(1), 92.8 (2); P(2)–Ir–C(2), 88.4 (2); P(2)–Ir–C(5), 90.3 (2); P(2)–Ir–C(75), 95.4 (2); C(1)–Ir–C(2), 96.1 (3); C(1)–Ir–C(5), 172.7 (3); C(1)–Ir–C(75), 91.5 (3); C(2)–Ir–C(5), 77.4 (3), C(2)–Ir–C(75), 171.3 (3); C(5)–Ir–C(75), 94.8 (3); Ir–C(2)–C(3), 114.9 (5); C(2)–C(3)–C(4), 115.3 (6); C(3)–C(4)–C(5), 115.9 (6); C(4)–C(5)–Ir, 115.2 (5)°.

$\overline{Ir(CR{=}CRCR{=}CR)}(PPh_3)_2(CO)(=\overline{C(CH_2)_3O})^+BF_4^-$, **2**, is obtained following workup. Similar reaction with **6** at 23 °C also generates **2**. In the $^{13}C\{^1H\}$ NMR spectrum ($CDCl_3$) of **2**, pseudo triplets are observed at δ 171 (J = 6, 8 Hz), 161 (J = 9, 12 Hz), and 140 (J = 8, 11 Hz). The analogous ^{13}CO-labeled complex allows assignment of the δ 171 resonance to the carbon atom of the CO ligand. In the $^{31}P\{^1H\}$ NMR spectrum of **2**, a singlet is observed at δ 11.0 which requires either a plane of symmetry containing the 2-oxacyclopentylidene ligand or rapid rotation about the iridium–carbene bond. We were unable to observe line broadening in the ^1H NMR resonances of the 2-oxacyclopentylidene ligand between −80 °C and +80 °C.

In order to structurally characterize this new class of metallacycle complex, a single-crystal X-ray diffraction study was performed on **2** (Figure 1).[8] The complex deviates from ideal octahedral geometry with the C(2)–Ir–C(5) angle constrained by the metallacycle ring to 77.4 (3)° and the trans PPh_3 ligands bent away from the carbene ligand toward C(2) of the metallacycle. The Ir–C(2) and Ir–C(5) bond distances of 2.108 (7) and 2.101 (7) Å are significantly longer than the 2.054 (4) Å Ir–C distance reported by Bergman for $(\eta^5\text{-}C_5Me_5)Ir(PMe_3)(H)(CH{=}CH_2)$.[9] In **2**, the plane of the 2-oxacyclopentylidene ligand bisects the plane of the metallacycle at an angle of 24°.[10]

Further reactivity of these unprecedented metallacycle–carbene complexes is currently under exploration with an emphasis on methods for inducing formation of cyclopentadiene products.

Acknowledgment. Partial support from the Monsanto Company and the Academic Senate at the University of California, San Diego is gratefully acknowledged.

Supplementary Material Available: Tables of analytical, NMR, and IR spectroscopic data for all new compounds, listings of fractional coordinates, bond distances, bond angles, hydrogen atom coordinates, and thermal parameters (8 pages); table of observed and calculated structure factors (30 pages). Ordering information is given on any current masthead page.

(8) Crystal data for **2** (293 K): $C_{53}H_{48}IrO_{10}P_2BF_4$, monoclinic, Cc, a = 12.723 (2) Å, b = 21.195 (4) Å, c = 18.432 (3) Å, β = 90.37 (1)°, V = 4970 (1) Å^3, Z = 4, D_{calcd} = 1.585 g cm^{-3}, μ = 29.8 cm^{-1}. A pale pink specimen (0.30 × 0.31 × 0.34 mm) was used for data collection (Nicolet R3m/μ, 4° ≤ 2θ ≤ 52°, Mo Kα). Of 5178 reflections collected, 5041 were independent (R_{int} = 1.8%), and 4748 with $F_o \geq 3\sigma(F_o)$ were considered observed and empirically corrected for absorption (T_{max}/T_{min} = 0.370/0.324). The Ir atom was located by heavy atom methods. During the final refinement the BF_4^- ion was constrained to a tetrahedral geometry with a common, refined B–F distance (1.222 (7) Å, ~0.13 Å shorter than normal), and the phenyl rings were constrained to rigid hexagonal rings. With all non-hydrogen atoms anisotropically refined and hydrogen atoms treated as idealized isotropic contributions: R(F) = 3.11%, R(wF) = 3.76%, all data R(F) = 3.47%, GOF = 1.018, Δ/σ = 0.08, $\Delta(\rho)$ = 1.8 eÅ^{-3} (0.90 Å from Ir), and N_o/N_v = 8.34. All computer programs and sources of scattering factors are contained in the SHELXTL program library (Nicolet Corp., Madison, WI).

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Measurement of High-Resolution NMR Spectra in an Inhomogeneous Magnetic Field

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Received August 18, 1986

Low homogeneity of the static magnetic field results in a broadening of the nuclear magnetic resonance (NMR) spectral transitions; this precludes NMR spectral analyses based upon the interpretation of the familiar NMR parameters, chemical shifts, and scalar coupling constants. Possible solutions to this problem can involve use of either zero-quantum coherence[1-4] (ZQC), or, alternatively, the *N*-type peaks produced by the SECSY experiment,[5,6] for which the line widths are independent of magnetic field inhomogeneity. However, neither technique produces the conventional spectrum of a spin system. A third alternative, which has been demonstrated for partially orientated liquids, uses total spin coherence transfer echoes[7,8] to produce the conventional spectrum of a spin system. Unfortunately, this elegant technique has two disadvantages which limit its application in isotropic liquids: at least one spin must be coupled to *all* the other spins in a given spin system to create the total spin coherence upon which the technique depends; furthermore, the more spins there are active in a coherence, the lower is the intensity with which it will be excited. Together these two considerations usually impose a practical upper limit of four to the number of spins active in any one coherence in an isotropic liquid. All three of the above options involve two-dimensional experiments,[9] and in each case only the F1 dimension is independent of magnetic field inhomogeneity.

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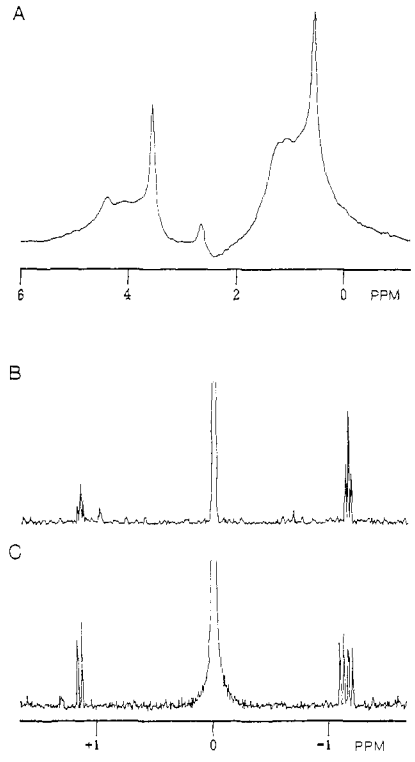

Figure 1. ^{1}H NMR (300-MHz) spectra of a 0.1 M solution of the AX_3 spin system L-alanine in D_2O acquired in an inhomogeneous magnetic field. (A) Conventional SQC spectrum; (B) SECSY spectrum (512 t_1 values, 1 scan each, F1 projection taken); (C) spectrum obtained with pulse sequence I (t_d = 300 ms, n = 0.5, 512 t_1 values, 8 scans each, F1 projection taken).

In this communication, we describe an alternative approach, based upon the SECSY pulse sequence, which produces high-resolution F1 spectra, even in an inhomogeneous magnetic field; such spectra exhibit conventional multiplets from which scalar coupling constants can be obtained. The pulse sequence is represented as

$$90°(x)-(t_d/2 + t_1/4)-180°(x)-(t_d/2 - t_1/4)-90°(\theta)-(nt_1/2)-180°(\theta)-(nt_1/2)-(t_1/2)-\mathrm{Acq}(\phi) \quad \text{(I)}$$

The phases θ and ϕ are cycled through $\theta = x,y,-x,-y$ and $\phi = x,-x,x,-x$, although in an inhomogeneous magnetic field phase cycling is redundant, as all unwanted coherences will dephase and hence not be observed.

Figure 1 shows the spectrum of the AX_3 spin system L-alanine in an inhomogeneous magnetic field produced by this pulse sequence, along with the corresponding conventional and SECSY spectra for comparison. Unlike the conventional spectrum (A), the spectrum (C) produced by our pulse sequence I is still at high resolution, and unlike the SECSY spectrum (B), it exhibits only conventional multiplets and coupling constants. However, as with SECSY, peaks only occur at plus and minus half the difference in the chemical shifts of the pairs of coupled spins. With the SECSY experiment, each pair of N-type peaks[6] is the result of the chemical shift and scalar coupling evolution of a pair of spins, whereas a peak produced by pulse sequence I, although the result of the chemical shift evolution of the two spins, involves the scalar coupling evolution of only *one* of the spins.[10-12] The result of this is that of each pair of N-type peaks one peak will exhibit the normal multiplet of one of the spins, giving rise to it, and the other will only exhibit the multiplet of the other. To facilitate easy analysis of the spectrum, the pulse sequence has been designed in such a way that the relative scales of the chemical shift and scalar couplings can be altered. Although it is actually the chemical shift which is being scaled down, the pulse sequence is constructed such that it appears that it is the scalar couplings which are being scaled up. This has the advantage that the t_1 increment does not have to be altered each time the relative scales of chemical shift and scalar couplings are altered. This scaling is determined by the factor n and results in an apparent J scale of $(n + 1/2)$; it is accomplished by the three intervals immediately after the second 90° pulse $\{(nt_1/2)-180°(\theta)-(nt_1/2)\}$.[10,13] If these intervals are omitted from the pulse sequence, the J scale will be $(1/2)$. Scaling can either be used to improve the digitization of the multiplets or to decrease the number of increments, and hence time, required to obtain the same digitization of the multiplets.

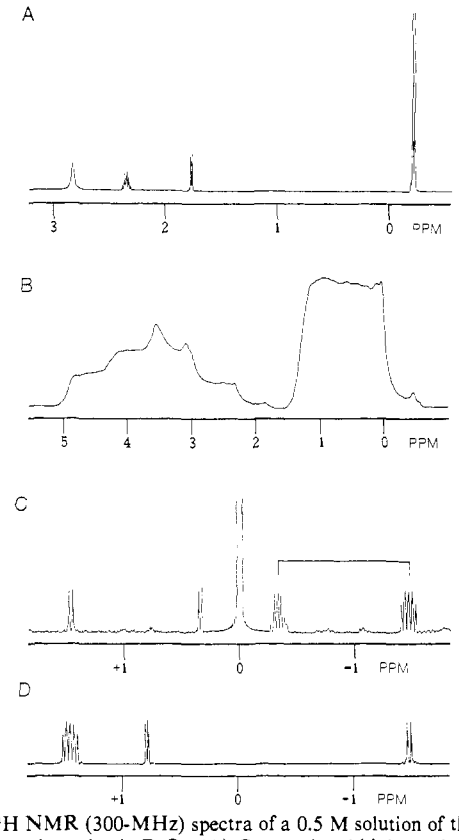

Figure 2. ^{1}H NMR (300-MHz) spectra of a 0.5 M solution of the AMX_3 spin system L-threonine in D_2O. (A) Conventional high-resolution SQC spectrum measured by using a homogeneous magnetic field. Spectra B–D were obtained in an inhomogeneous magnetic field; (B) conventional SQC spectrum; (C) spectrum obtained with pulse sequence I with identical multiplets indicated (t_d = 340 ms, n = 0.5, 704 t_1 values, 8 scans each, F1 projection taken); (D) SQC spectrum reassembled from (C) according to method described in text. The base line is artificial.

If a spin is associated with several different N-type peak pairs, in each case one peak of each pair will exhibit the multiplet of that spin. This facilitates the elucidation of scalar coupling networks. In addition, the splittings in the negative-frequency peak will always correspond to those of the spin which has the lower field chemical shift. As a consequence of this, the relative chemical shifts of whole spin systems, rather than just pairs of spins, can be determined. Visually, the conventional (single-quantum coherence) spectrum of a spin system may be reassembled in three steps: first, the peak at 0.0 Hz is removed; second, peak pairs are moved horizontally, keeping the frequency difference between each pair of peaks constant, until all identical multiplets overlap; finally, the spectrum must be reversed (reflected about 0.0 Hz). This is demonstrated for the AMX_3 spin system L-threonine in Figure 2.

The value of t_d is fixed for a given experiment. It may have any value above a minimum determined by N (the number) and Δt_1 (the size) of t_1 increments, according to the expression $t_d \geq N\,\Delta t_1/2$. Peak intensities are dependent upon t_d and the scalar

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couplings of a spin system. Consequently, spectra obtained with several values of t_d may have to be coadded to obtain the complete spectrum. Conversely, if several peaks do overlap, this dependency may be used to resolve them.

With this experiment, a high-resolution spectrum can be acquired using a magnetic field of such low homogeneity that a conventional spectrum would contain no useful information. It appears that this experiment is not bound by the limitations discussed above for the total spin coherence transfer echo technique in isotropic liquids. It is certainly superior to both zero-quantum coherence and SECSY spectra in that it produces single-quantum scalar coupling constants which would otherwise be unobtainable and simultaneously facilitates both the mapping of scalar coupling networks and the reassembly of the conventional (single-quantum coherence) spectrum of the spin system. We envisage that it will prove useful both in the context of in vivo NMR spectroscopy and in other areas for which low magnetic field homogeneity is unavoidable. Such applications, along with a detailed analysis of the pulse sequence will be given elsewhere.

Acknowledgment. We wish to thank Dr. Herchel Smith for an endowment (L.D.H) and for a research studentship (T.J.N.). This work was carried out while T.J.N. was a visitor at Varian Associates' NMR Applications Laboratory, Palo Alto, CA, which was made possible in part by a travel grant from the research fund of Jesus College, Cambridge; we thank Drs. Steve Patt and Evan Williams for their hospitality.

The Structure and Synthesis of Dolastatin 3[1a]

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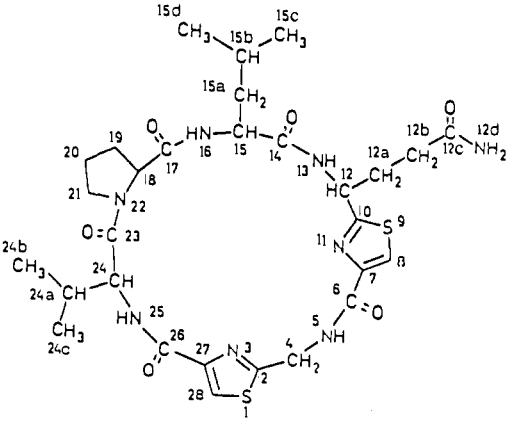
Received May 26, 1987

Because of the P388 lymphocytic leukemia (PS) cell growth inhibition displayed by dolastatin 3,[2] an unusual cyclic pentapeptide containing two thiazole amino acid units, its complete structure has been the focus of intensive interest. In 1979 we isolated ca. 1 mg of amorphous dolastatin 3 from 100 kg (wet wt) of the Indian Ocean sea hare *Dolabella auricularia*. On the basis of interpretation of results from the best instrumental techniques then available to us, and presuming an all L-configuration, structure **1** was tentatively assigned.[2] Later we[3a] and

cyclo[Pro-Leu-Val-(gln)Thz-(gly)Thz]
1

others[4] eliminated structure **1**, the chiral isomers,[3a,4] the reverse order of bonding,[3b,4] and a modified[3c,5] amino acid sequence by total syntheses.[6] When the remaining few micrograms of dolastatin 3 decomposed in storage, efforts directed at reisolation were begun and completed in mid 1986. Reisolation proved to be even more challenging and afforded only 1.8 mg [1.8×10^{-6}% yield, mp 155–159 °C, $[\alpha]^{29}_D$ −48.5 (*c* 0.01, CH_3OH)] of this sensitive peptide.[7] But by in-depth utilization of current advances in high field (400 and 500 MHz) ^1H NMR and other necessary techniques we now report unequivocal structure **2** for dolastatin 3 and total synthesis of this very interesting substance.

Acid hydrolysis (6 N HCl, 110 °C, 24–72 h) of natural (−)-dolastatin 3 (**2**) and examination of the hydrolysate (as *N*-trifluoroacetyl-*n*-butyl ester derivatives) by chiral gas chromatographic (fused silica column coated with "Chirasil-Val") analysis indicated that the Val, Pro, and Leu units all belonged to the L-configurational series. However, the configuration of (gln)Thz could not be ascertained and was solved by the synthetic routes to follow. Results of a two-dimensional NMR study[8] using ^1H,^1H



cyclo[L-Val-L-Pro-L-Leu-L-(gln)Thz-(gly)Thz], dolastatin 3
2

Table I. Dolastatin 3 Assignments in Deuteriochloroform Solution Relative to Tetramethylsilane for ^1H,^1H Connectivity by NOE Experiments

positn irradtd	^1H chemcl shift, ppm	connctvty by ^1H-[^1H] NOE diffrnce	% NOE
25	8.32	N25H, C24H	0.8
		N25H, C24cH	0.8
24	4.75	C24H, C24bH	1.1
		C24H, C24cH	1.1
		C24H, C21H	2.7
18	3.97	C18H, N16H	1.3
		C18H, C19H	0.8
16	6.01	N16H, C18H	4.1
		N16H, C15H	3.3
13	7.85	N13H, C15H	0.8
		N13H, N16H	0.8
		N13H, C12H	1.0
		N13H, C12aH	1.1
12	5.54	C12H, C12aH	2.3
		C12H, C12bH	1.3
12d	5.42	N12d, C12bH	0.5
	6.25	N12d, C12bH	0.7
5	8.76	N5H, C4H	1.2
		N5H, C4H	1.7
4	5.23	C4H, N5H	0.8

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(7) The physical properties (e.g., the 400-MHz ^1H NMR spectrum) were identical with those previously reported (ref 2).

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