fination of a ketone was possible by limiting the amount of reagent (entry 7).

This new olefination method appears to proceed through a novel mechanism. The facile thermolysis[13,18,19] of **5** was previously reported to take place via the intramolecular elimination of methane and the formation of **1**. Subsequent reversible H abstraction from a Cp ring forms a species equivalent to Cp-(C_5H_4)TiMe, finally leading to unidentified titanium products. Despite this behavior of **5** in the solid state and in solution,[20] we have found by NMR spectroscopy that it survived prolonged heating in the presence of **6**. Although this may be due to complexation of **5** with **6**, we could not confirm it. Trapping of an autocatalytic intermediate such as **1** by **6** or stabilization of **5** by other species is also possible. Addition of ligands (Me_3P, $(EtO)_3P$, DMAP) that could stabilize or induce formation of **1** resulted in similar or lower product yields.

Olefination of acetophenone and benzophenone with $Cp_2Ti(CD_3)_2$, **8**, took place with complete deuterium incorporation, suggesting that Cp hydrogen abstraction is not involved. Surprisingly, however, the reaction of **8** with dodecyl acetate showed only ca. 50% of deuterium at C-1 while a significant amount of deuterium was detected at C-3. Similarly, the methylenation of dodecyl acetate-d_3, **9**, with **5** indicated the presence of deuterium at C-1 and hydrogen at C-3 (including some CH_3), but only to the extent of 5-10%. Complete deuteration was observed in the reaction of **8** with **9**, confirming the lack of Cp hydrogen participation.

These results suggest an alternative non-carbene mechanism involving carbonyl complexation to **5** followed by methyl transfer to the carbonyl. The resulting adduct may then undergo loss of methane and "titanocene oxide" to form the olefinic bond. This type of methyl transfer, common to more acidic organotitanium reagents such as Me_2TiCl_2,[4] may also occur during the reactions of **5** with other electrophiles.[14] The observed differences in the reactivity of esters from ketones may be due not only to pertinent thermodynamic reasons but also to a different conformational geometry of their titanium complexes.[21] Participation of the second carboxylate oxygen in esters may also lead to a different intermediate that allows the observed H/D scrambling to take place.

In summary, we have shown that the aluminum-free reagent **5** serves as an alternative to the Tebbe and Grubbs reagents for the methylenations of aldehydes, ketones, esters, and lactones. Similar olefinations were also accomplished with other titanocene homologues.[22] Additional investigations on the reactions of dialkyltitanocenes with carbonyl substrates are currently under way.

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Three-Dimensional Nuclear Magnetic Resonance Approach to Multiple-Quantum-Filtered Correlated Spectroscopy and Its Application to Proteins

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The elucidation of protein structures using NMR spectroscopy relies on the identification of amino acid spin systems. This has been greatly facilitated by the introduction of multiple-quantum-filtered correlation spectroscopy (MQF-COSY).[1-3] This communication describes a three-dimensional (3D) experiment which performs a straightforward time-saving acquisition of the usual double quantum filter, triple quantum filter, ..., *n*-quantum filter COSY 2D spectra and its application to a protein.

All 3D experiments proposed so far are based on the same principle:[4] two 2D experiments, E1 and E2, decomposed along the general scheme (preparation, evolution, mixing, and detection periods[5]), merged into a single 3D experiment. The evolution, mixing, and detection periods of E2 replace the detection period of E1. However we considered that most 2D experiments could be generalized into a 3D one by the introduction of any variable quantity (possibly other than a time) in its mixing period that leads to an additional phase or amplitude modulation of the detected signal. In the present case we introduce a phase variation during the mixing period of the MQF-COSY experiment.

The basic 2D MQF-COSY pulse sequence

$$90°_{\phi} - t_1 - 90°_{\phi+\psi}\ 90°_{\psi} - t_2 - \qquad (1)$$

is thus transposed in the following 3D experiment:

$$90° - t_1 - 90° - \theta - 90° - t_2 - \qquad (2)$$

t_1 is the evolution period of the experiment and is varied in the normal way, and t_2 is the acquisition time. The third variable quantity is the phase difference between the last two pulses: θ is incremented independently in steps $\Delta\theta$. A 3D array (t_1, θ, t_2) is thus recorded. A three-dimensional Fourier transformation yields a 3D spectrum $F1 \times P \times F2$. $F1$ and $F2$ are the usual frequency dimensions and P is a dimension displaying the transition order.

The phase difference θ between the last two pulses results in the phase modulation by a factor $\exp(jp\theta)$ of the contribution of the p-quantum transitions to the recorded signal. The phase cycling procedure in the usual *n*QF 2D experiment merely consists in the cancellation of the unwanted p-quantum contributions, with $-n < p < +n$, through an in situ linear combination. A phase cycle of at least $2n$ steps is necessary. Successive recording of one-, two-, ..., *n*-quantum-filtered COSY spectra therefore results in a total of $n(n+1)$ scans for each t_1 value.

As already noticed,[5,6] it is redundant to perform successively double-, triple-, ..., *n*-quantum-filtered experiments: one only needs to record n different 2D data sets successively with $\theta = 0, \pi/n$, ..., and $\pi(2n-1)/n$ and combine them with appropriate digital phase corrections. This leads to complicated handling and storage of data, as mentioned earlier.[6]

A simple 3D Fourier transform can, however, restore the various contributions without such difficulties. It is possible to sequencially

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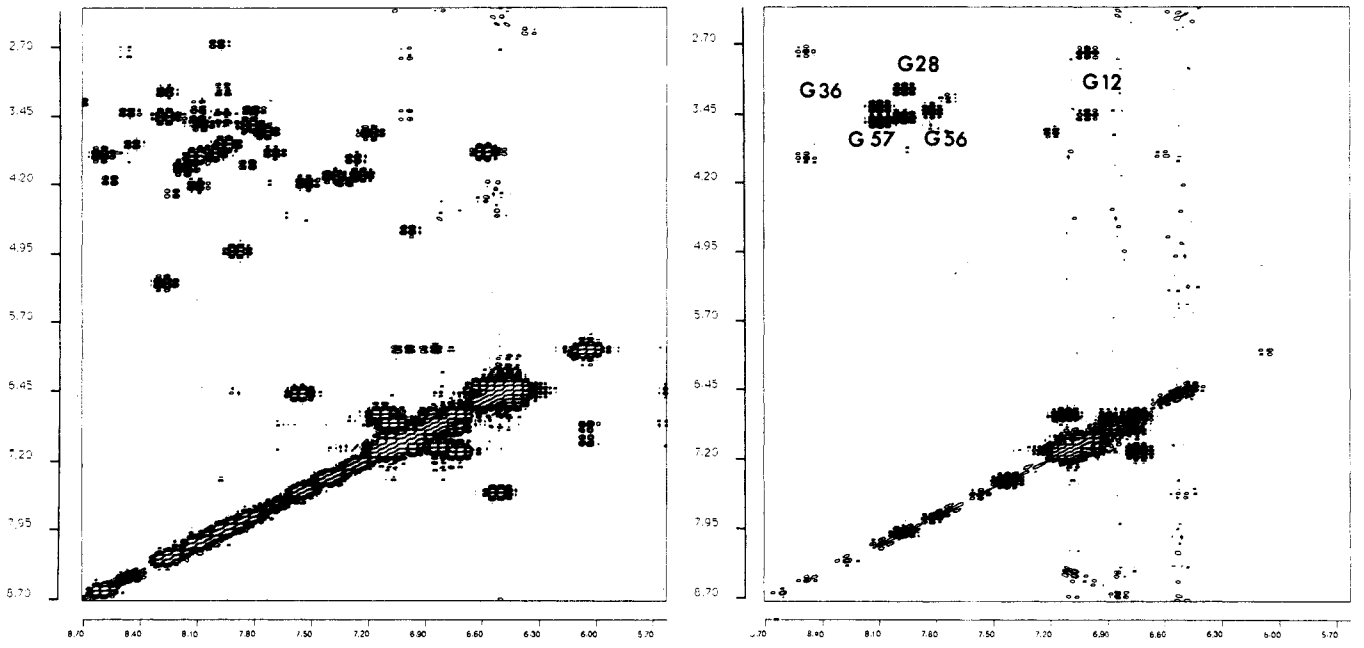

Figure 1. Low-field region of the ($F1$, 2, $F2$) (left) and ($F1$, 3, $F2$) (right) planes. The sample was 10 mM BPTI in H_2O, pH = 3.4, 20 °C. The experiment performed used pulse sequence 2 proposed in the text, and θ was varied in $\pi/8$ steps from 0 to $15\pi/8$. The experiment consisted of 512 t_1 increments × 16 phase increments, and eight scans of 2K acquisition points were acquired for each FID on a Bruker AM400 instrument. A two-step phase cycle was used for each t_1, allowing suppression of the signal arising from the relaxation during t_1. A real to complex FT was applied in all three dimensions. TPPI was used in the $F1$ dimension, and the spectra are in the phase-sensitive mode in all three dimensions. The cross peaks are identified by one-letter symbols for the amino acid residues and their sequence positions.

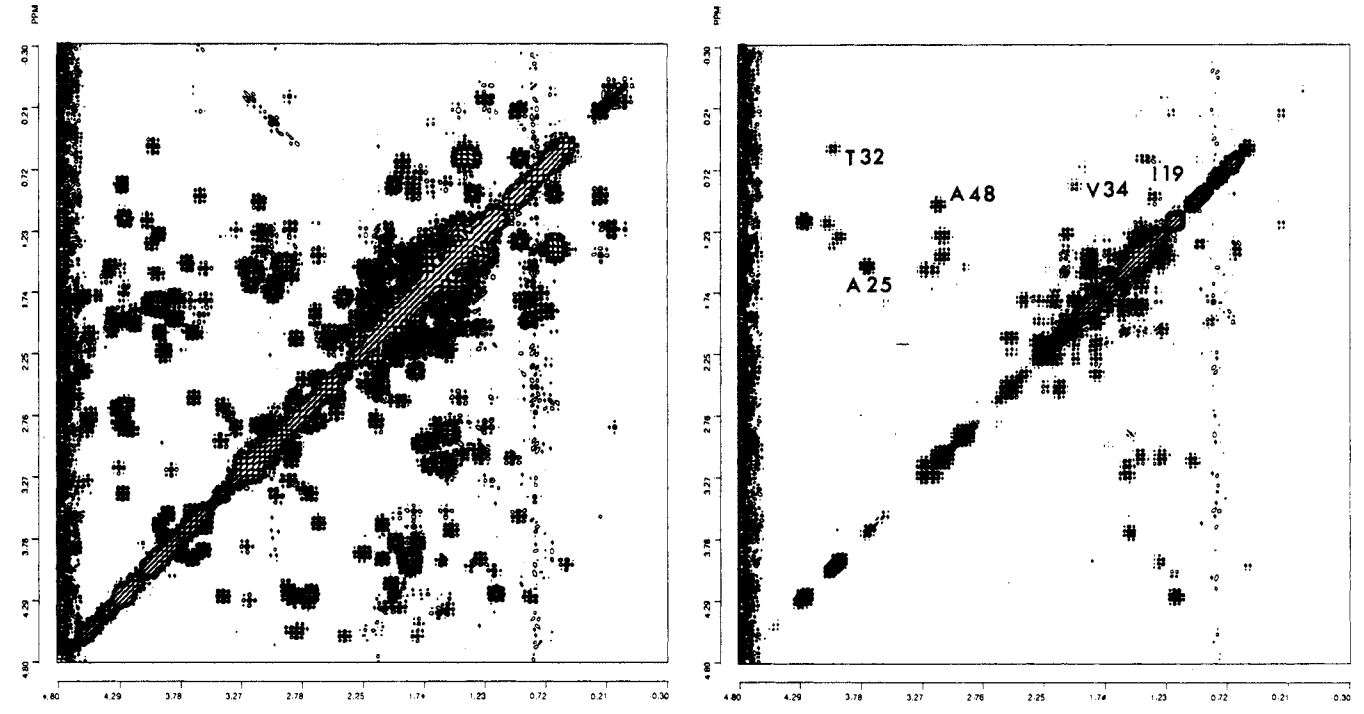

Figure 2. High-field region of the ($F1$, 3, $F3$) (left) and ($F1$, 4, $F3$) (right) planes.

store each 2D experiment in a 3D data set. The quantum information appears as a phase modulation along the θ direction of the 3D set. A classical FT can be applied along this axis. Quadrature in the quantum dimension is naturally achieved by this experiment, leading to a separation of the $+p$ from the $-p$ quanta. A simple folding of the data along $P = 0$ suppresses this separation. Any phase imperfections or instabilities will result in noise along the P dimension; thus phase increments smaller than the necessary ones[7] may improve the spectrum quality. On our Bruker AM spectrometer, however, due to the quality of the phase shifter, no significant gain could be achieved.

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In order to test its general applicability, this new 3D experiment has been performed on a sample of basic pancreatic trypsin inhibitor (BPTI). Transitions up to eight quanta were separated by the use of $\pi/8$ phase steps. Total measuring time was 24 h. This corresponds to a theoretical gain in acquisition time of 72 h over a separate acquisition of the corresponding 2D experiments. Figures 1 and 2 exemplify some of the advantages of this experiment:[3] the 3QF spectrum (Figure 1) displays the αH–NH cross peaks of glycines 12, 36, ..., which are thus clearly separated from the rest of the fingerprint region, as well as peaks arising from side-chain NH_2 protons. The aliphatic region of the 4QF spectrum (Figure 2) provides a clear display of cross peaks arising from alanines, threonines, and other long side chain residues.

The proposed approach, based on the 3D NMR concept, presents all the advantages of the Fourier transform over any filter-based experiment (simplicity, acquisition time saving, improved resolution, compensation for phase imperfections, and oversampling capabilities[7]) and benefits from the recent developments of 3D NMR software.[8] Its wide-range applicability is demonstrated through the protein NMR experiments here described. Moreover, it generalizes the construction of 3D NMR experiments, the third variable parameter being no longer restricted to a time.

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Conjugated Ketenes: Cyclopropyl, Alkenyl, Alkynyl, and Acyl Substituents

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The chemistry of ketenes has been receiving increasing attention,[1-3] but the way in which substituents affect the stability and reactivity of ketenes is not well understood. Conjugating substituents are of particular interest,[3a] and reports[3] of the first preparations of alkynylketenes[3e] have recently appeared, although these species were not directly observed. There has been continued study of alkenyl-,[1e,2b,4] cyano-,[5] and acylketenes.[6] Despite longstanding interest in cyclopropyl conjugation with alkenes,[7] the only cyclopropylketenes previously studied were reactive intermediates.[8] However, there has been no systematic effort to understand the way in which these conjugating substituents affect the properties of ketenes, so we have initiated theoretical studies of this series. We also report here the first isolation and direct observation of cyclopropylketenes, the simple generation and trapping of hydrocarbon-substituted alkynylketenes, and kinetic measurements of the reactivity of an acylketene.

Table I. Rates of Hydration in H_2O/CH_3CN of c-PrCPhC=O (**4**) and c-Pr_2C=C=O (**6**) at 25 °C

H_2O		k_{obsd}, s^{-1}		[HCl],[a] M	
vol. %	[H_2O], M	**4**	**6**	(20% H_2O)	k_{obsd}, s^{-1}
10	5.56	0.0930	0.0102	0.806 (**4**)	0.138
20	11.1	0.297[b]	0.0486[c]	1.21 (**4**)	0.400
30	16.7	0.514	0.112	0.0102 (**6**)[d]	0.0638
40	22.2	0.728	0.200[c]	0.0204 (**6**)	0.0799
50	27.8		0.406[c]	0.0307 (**6**)	0.0978
				0.0409 (**6**)	0.110
				0.0511 (**6**)	0.123

[a] μ = 0.05 (NaCl). [b] For *i*-PrCPh=C=O,[2b] $k(H_2O)$ = 0.712 × 10^{-3} s^{-1}. [c] For Et_2C=C=O,[2d] $k(H_2O)$ = 0.0492, 0.196, and 0.357 s^{-1} in 20, 40, and 50% H_2O/CH_3CN, respectively. [d] k_{obsd} = 1.46(M^{-1} s^{-1})[H^+] + 0.0502; for Et_2C=C=O,[2d] k_{H^+} = 30.1 M^{-1} s^{-1}.

Ab initio molecular orbital calculations of the isodesmic reaction

$$RCH{=}C{=}O + CH_3CH{=}CH_2 \rightarrow CH_3CH{=}C{=}O + RCH{=}CH_2$$

were carried out to compare the effect of various conjugating substituents relative to CH_3 in stabilizing the alkenyl bond of ketene compared to that of ethylene. At the 3-21G//3-21G level with optimized geometries values of ΔE (kcal/mol) for different R groups for this reaction are −1.9 (c-Pr), −0.1 (HC≡C), −0.2 (CH_2=CH), and 3.3 (O=CH). Thus formyl is relatively more stabilizing for ketene, whereas the cyclopropyl substituent is favored as a substituent on ethylene. Higher level calculations are in progress, but the 3-21G results suggest that there are no extraordinary effects of substituents on ketene stability. Our calculations agree with related work[6h] which appeared since submission of this manuscript.

All four of these substituents are σ-electron withdrawing, formyl is also a strong π acceptor, and C_β of ketene is negatively charged,[2a,f] so the relative stabilizing effect of formyl may be due to conjugation. The net substituent effect on ketene reactivity will also depend on how the substituents affect the different transition states for reaction, but on the basis of the ground-state influences, the conjugated ketenes appear likely to be comparable in accessibility to the well-studied alkylketenes.

For the preparation of ethynylketenes, 2-alkyl-4-phenylbutynoic acids (**1**, eq 1)[9] were converted to acid chlorides, which reacted readily even at −78 °C with triethylamine to give yellow colors presumably due to the alkynylketenes **2** (eq 2), but after warming to 25 °C IR measurements did not reveal any residual ketenes. When **2** were generated in the presence of cyclopentadiene, the cycloaddition products **3** formed as single stereoisomers (eq 3) with the larger alkyl group assigned to the endo positions, as established for ketene cycloadditions with cyclopentadiene[4h,10a] and vinyl ethers.[10b]

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