Chart I

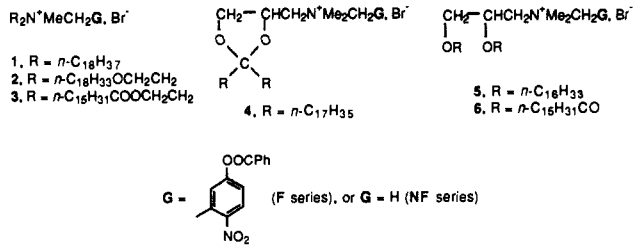


Table I. Dynamics of Covesicular Systems

covesicle[a]	d,[b] nm	T_c, °C	k_f,[c] s^{-1}	k_s,[c] s^{-1}	$t_{1/2}$ flip
1[d]	48	39	0.17	0.0018	>1 h/25 °C; 2 min/38-40 °C
2	27	37	0.32[e]	0.055	4 min/25 °C; 1 min/30 °C
3	29	40	0.42[e]	0.0039	20 min/30 °C; 1-2 min/35 °C
4	44	31	0.067	0.0018	3 min/35 °C; 1 min/40 °C
5	48	37	0.075	0.0010	5 min/40 °C; 1 min/45 °C
6	41	44	0.053	0.000062	5 min/55 °C; 1 min/65 °C

[a] See text for structures and compositions.[9] [b] Diameters from dynamic light scattering at pH 4, 0.01 M KCl. [c] k_f and k_s were determined at 25 °C. [d] See refs 4a and 4b. [e] By stopped-flow spectroscopy.

Covesicles of surfactants **1-F/1-NF** to **6-F/6-NF** were created by sonication of $CHCl_3$-cast films of surfactant mixtures in pH 3.9 aqueous HCl, containing 0.01 M KCl.[9] The gel to liquid crystal phase transition temperatures (T_c) of the covesicles were determined from temperature-dependent discontinuities in the fluorescence polarization of covesicalized 1,6-diphenyl-1,3,5-hexatriene;[4,10] cf. Table I.

For flip-flop studies, the covesicles were first surface-differentiated by exposure to 1×10^{-4} M glutathione in 0.01 M pH 8 Tris buffer (0.01 M in KCl) at 25 °C. These reactions rapidly (k_f) converted the covalently bound, *exovesicular* *p*-nitrophenyl benzoate moieties (**G**) of **1-F** to **6-F** to *p*-nitrophenolates (**G'** or **9**), as monitored spectroscopically at 400 nm. If the reactions were allowed to continue, slower, H^+/OH^- *permeation-limited*,[4] *endovesicular* cleavages of **G** to **G'** were observed with rate constants k_s.[4] Values of k_f and k_s appear in Table I.[11] To assess flip-flop, the external pH was reduced to 3.9 (HCl) immediately after completion of the exovesicular reaction, quenching further benzoate cleavage.

The surface-differentiated covesicles were warmed to a selected "incubation" temperature, for a specific time to induce flip-flop; cooled back to 25 °C; and then readjusted to pH 7.9 (NaOH). The *new, fast* (k_f) appearance of *p*-nitrophenolate, initiated by the pH change, represented the cleavage of those surfactant **G** moieties that had "flipped" from endo- to exovesicular loci during the incubation procedure.[12] The subsequent, residual k_s reaction was due to the cleavage of still-intact, endovesicular **G** groups. In all cases, the absorptions of **G'** released in the initial k_f and postincubation k_f and k_s reactions summed to the stoichiometric value. The extent of flip-flop equilibration induced by incubation was revealed by the **G'** absorptions attending the postincubation k_f and k_s reactions. By exploring different incubation times and temperatures, we obtained approximate half-times for the flip-flop equilibrations of the surface-differentiated covesicles; cf. Table I.

The $t_{1/2}$ data demonstrate correlations between surfactant molecular structure and monomer stability toward transverse redistribution within the bilayer. The bilayer stabilities of simple double long chain ammonium ion surfactants increase with chain length and diminish abruptly at T_c, where bilayer rigidity relaxes.[4b,13] An ether oxygen near the head group (**2**) enhances the ease of flip-flop, relative to **1** of similar chain length, whereas bilayers of the related ester (**3**) are considerably more stable than those of **2** and similar to **1**. Ether oxygen may reduce the hydrophobic bonding contributions of neighboring CH_2 groups, reducing both the lipid's effective chain length and bilayer stability,[14,15] whereas acyl moieties may stabilize bilayers via carbonyl-water H-bonding networks.[14,15] Bilayers of **2** and **3** display rapid flip-flop at $T \lesssim T_c$.

Ketal surfactant **4** is a structural bridge between "geminal" double long chain surfactants **1-3** and "vicinal", glycerol-derived surfactants **5** and **6**. Bilayers of **4** display modest stability *above* T_c and are thermally more resistant to flip-flop than those of ether surfactant **2**. "Opening" the cyclic ketal structurally transposes **4** to **5**, affording bilayers of still greater resistance to flip-flop. Bilayers of **5** manifest stability above T_c, while the enhanced stability of ester vs ether lipid bilayers is again apparent in the **6** vs **5** comparison. Bilayers of **6** are quite stable at T_c and require elevated temperatures to induce rapid flip-flop, as is the case with vesicles of egg lecithin or dipalmitoylphosphatidylcholine.[2]

The sensitivity of monomer dynamics within the membrane to molecular structure, in bilayers constructed of lipids **1-6**, is noteworthy and suggests that related methodology could be used to effectively model the behavior of biologically relevant artificial membranes.

Acknowledgment. We are grateful to Professor D. A. Jaeger for a gift of the ketal bromide precursor of **4** and to the U.S. Army Research Office for financial support.

(9) The general procedure is described in ref 4a. The **F/NF** molar ratios were 1:10 for **1** and 1:7 in all other cases. The total [surfactant] was 4×10^{-4} M. The sonication methods employed here apparently produce unilamellar vesicles.[4a] Observed mean diameters of the covesicles (Table I) are compatible with this idea.

(10) Andrich, M. P.; Vanderkooi, J. M. *Biochemistry* **1976**, *15*, 1257. Moss, R. A.; Swarup, S. *J. Org. Chem.* **1988**, *53*, 5860.

(11) The distributions of exovesicular and endovesicular reactions were (ca.) 50/50 (**1**), 65/35 (**3**, **4**), and 70/30 (**2**, **5**, **6**).

(12) The methodology, as applied to **1-F/1-NF** covesicles, is described in detail in ref 4a. Note that some exovesicular (**G'**) surfactant molecules must "flop" to endovesicular loci during incubation.[4a]

(13) To obtain $t_{1/2}$ values of 1-12 min requires temperatures ($\sim T_c$) of 25, 39, and 50 °C, respectively, for **1**, R = $C_{16}H_{33}$, $C_{18}H_{37}$, or $C_{20}H_{41}$.[4b]

(14) Tirri, L. J.; Schmidt, P. C.; Pullarkat, R. K.; Brockerhoff, H. *Lipids* **1977**, *12*, 863. The enhanced permeabilities of vesicular **2** or **5** (vs **3** or **6**, respectively) are related, expected consequences of their ether (vs ester) lipid structures.

(15) See also: Wong, P. T. T.; Mantsch, H. H. *Chem. Phys. Lipids* **1988**, *46*, 213. Ruocco, M. J.; Siminovitch, D. J.; Griffen, R. G. *Biochemistry* **1985**, *24*, 2406.

Titanium-Mediated Carbonyl Olefinations. 1. Methylenations of Carbonyl Compounds with Dimethyltitanocene

Nicos A. Petasis* and Eugene I. Bzowej

Department of Chemistry
University of Southern California
Los Angeles, California 90089
Received November 14, 1989

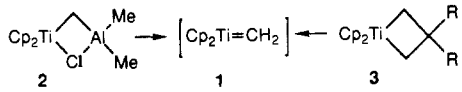
The methylenation of aldehydes and ketones is a useful synthetic transformation, performed with Wittig-type reagents,[1] with geminal dimetallic derivatives ($L_nM^1CH_2M^2L_m$) or with nucleophilic metallocarbenes ($L_nM{=}CH_2$).[2] Similar conversions of esters or lactones to enol ethers are normally not possible with most of these reagents.[3] An exception is the titanocene methy-

(1) (a) Cadogan, J. I. G., Ed. *Organophosphorous Reagents in Organic Synthesis*; Academic Press: London, 1979. (b) Bestman, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 65. See also: (c) Johnson, C. R.; Shanklin, J. R.; Kirchhoff, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 6462. (d) Welch, S. C.; Log, J.-P. *J. Org. Chem.* **1981**, *46*, 4072. (e) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

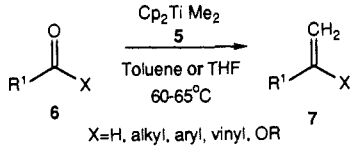
(2) (a) Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G. *Tetrahedron* **1970**, *26*, 1281. (b) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417; **1985**, *26*, 5579, 5581; *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698. (c) Kauffmann, T.; Konig, R.; Pahde, C.; Tannert, A. *Tetrahedron Lett.* **1981**, *22*, 5031. (d) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293. (e) Eisch, J. J.; Piotrowski, A. *Tetrahedron Lett.* **1983**, *24*, 2043. (f) Kauffmann, T.; Abeln, R.; Welke, S.; Wingbermuehle, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 909. (g) Piotrowski, A. M.; Malpass, D. B.; Bolewaski, M. P.; Eisch, J. J. *J. Org. Chem.* **1988**, *53*, 2829. (h) Tour, J. M.; Bedworth, P. V.; Wu, R. *Tetrahedron Lett.* **1989**, *30*, 3927.

0002-7863/90/1512-6392$02.50/0

lidene complex, **1**,[4] generated either from Tebbe's reagent,[5-8] **2**, or from Grubbs' titanacyclobutanes,[6,7a,9] **3**.

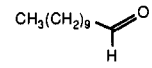
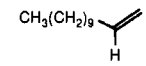
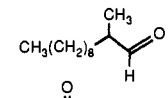
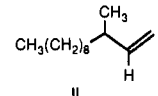
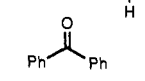
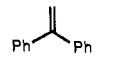
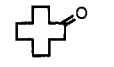
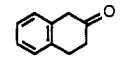
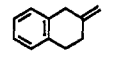
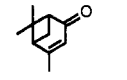
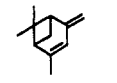
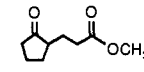
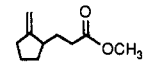
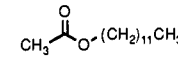
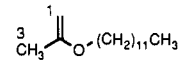
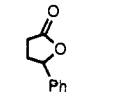
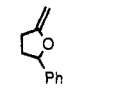
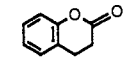
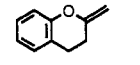
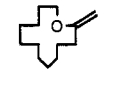


We report herein an alternative and more practical titanium-mediated methylenation that avoids some difficulties[10] associated with **2** and **3**, particularly for routine synthetic applications. This aluminum-free method involves dimethyltitanocene, **5**, a reasonably stable compound[11] readily prepared[12] from methyllithium and titanocene dichloride (Cp_2TiCl_2, **4**). Although **1** was postulated as an intermediate from the thermolysis of titanocene derivatives,[13] to our knowledge the methylenating ability of **5** has not been previously demonstrated.[14]



Thus, upon heating to 60–65 °C a toluene solution of **5** and a carbonyl compound, **6**, clean conversion to the corresponding olefin or enol ether, **7**, was observed[15] (Table I). This convenient and synthetically useful process required at least 2 equiv of **5** for complete conversion. Greater efficiency and increased reaction rates were noted when THF was used as the solvent,[16] suggesting the involvement of polar intermediates. A nonaqueous workup procedure simplified product isolation.[15]

Table I. Carbonyl Methylenations with **5**

Entry	Carbonyl compd	Product[a]	Yield %[b]
1			43
2			62
3			90[c]
4			83[d]
5			60
6			61
7			60[e]
8			65[d,f]
9			41
10			80
11			70

[a] Reactions were run in toluene with 3 equiv of **5** at 60–65 °C over 12–26 h on a 1-mmol scale. All products gave satisfactory IR, ^1H NMR, and ^{13}C NMR data. [b] Yields (not optimized) were determined after chromatographic purification. [c] Reference 16. [d] Reaction was also performed with 2 equiv of **5** in THF with a slightly higher yield. [e] One equivalent of **5** was used. [f] Reaction was carried out on a 10-mmol scale in toluene.

Despite increased steric hindrance, the α-disubstituted aldehyde (entry 2) gave a higher yield than its parent derivative (entry 1), presumably due to slower decomposition of the aldehyde moiety or the resulting olefin.[17] A variety of ketones (entries 3–7) including aryl, alicyclic, and α,β-unsaturated, were efficiently methylenated under these conditions. As with **2**[7] and **3**,[7a] but not with the Wittig reagents, readily enolizable ketones were smoothly olefinated (entry 5). Although esters (entry 8) and lactones (entries 9–11) were similarly converted to the corresponding enol ethers, this reaction was generally slower. Chemoselective ole-

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(8) (a) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. (b) Stevenson, J. W. S; Bryson, T. A. *Tetrahedron Lett.* **1982**, *23*, 3143. (c) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1983**, *48*, 1829. (d) Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395. (e) Kinney, W. A.; Coghlan, M. J.; Paquette L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7352. (f) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855. (g) RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458. (h) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565. (i) Adams, J.; Frenette, R. *Tetrahedron Lett.* **1987**, *28*, 4773. (j) Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768. (k) Clark, J. S.; Holmes, A. B. *Tetrahedron Lett.* **1988**, *29*, 4333. (l) Barrett, A. G. M.; Bezuidenhoudt, B. C.; Gasiecki, A. F.; Howell, A. R.; Russell, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 1392.
(9) (a) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907 and references therein. (b) Ott, K. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 5922. (c) Meinhart, J. D.; Anslyn, E. V.; Grubbs, R. H. *Organometallics* **1989**, *8*, 583.
(10) These include the high cost of commercially available **2** (ca. $100/g or $30/mmol), the long preparation times, the short shelf life, the need for special techniques due to extreme sensitivity to air and water, and residual aluminum reagents.
(11) It can be exposed to water during the normal workup procedure or to air during weighing and handling. This reagent can be stored in the dark as a toluene or THF solution for several months without significant decomposition, as indicated by NMR. As a solid, however, this light-sensitive compound decomposes rapidly.
(12) Claus, K.; Bestian, H. *Justus Liebigs Ann. Chem.* **1962**, *654*, 8.
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(14) For reactions of **5** with other electrophiles, see: (a) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**,, *33*, 181. (b) Kolomnikov, I. S.; Lobeeva, T. S.; Vol'pin, M. E. *Zh. Obshch. Khim.* **1972**, *42*, 2232. (c) Puddephatt, R. J.; Stalteri, M. A. *Organometallics* **1983**, *2*, 1400.
(15) Experimental procedure: A 0.5 M toluene (or THF) solution of Cp_2TiMe_2 (2–3 equiv) was mixed with the carbonyl compound (1 mmol) and stirred under argon in the dark at 65 °C. After the reaction was completed (12–26 h), the mixture was diluted with petroleum ether. The resulting yellow-orange precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica or basic alumina (for vinyl ethers).
(16) An NMR experiment with 2 equiv of **5** and benzophenone in THF showed consumption of the ketone after 2.5 h using only 1 equiv of **5**. On prolonged heating the remainder of **5** decomposed slowly while the olefin product remained unchanged. With only 1 equiv of **5**, however, the reaction was much slower (after 50 h both reactants were present). This may suggest that a second equivalent of **5** either participates in the reaction or is consumed by the titanocene oxide byproduct.
(17) It is likely, as a referee pointed out, that if **1** is the intermediate it could form a titanacyclobutane with the olefin. However, we did not detect such species either by NMR or by the formation of a dimethyl derivative upon hydrolytic workup.

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

Michel Robin, Marc-André Delsuc, Eric Guittet,* and Jean-Yves Lallemand

Laboratoire de Résonance Magnétique Nucléaire ICSN-CNRS, 91190-Gif sur Yvette, France

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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 $\theta = 0, \pi/n, \ldots,$ 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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