A Conformationally Rigid Acyclic Molecule

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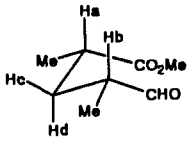
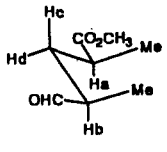
Received July 2, 1990

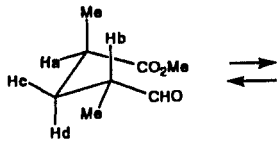
It is widely accepted that the reaction of acyclic molecules generally proceeds with low stereoselectivity because of their conformational flexibility.[1] To overcome this difficulty, the acyclic stereocontrol based on Lewis acid mediated chelation which locks the conformation has been often used in modern organic synthesis.[2] We report the first example of a conformationally rigid acyclic molecule; meso dimethylglutaric hemialdehyde **1** adopts a rigid conformation in solution without any assistance of chelating reagents.

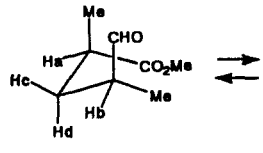


1, meso isomer



1'



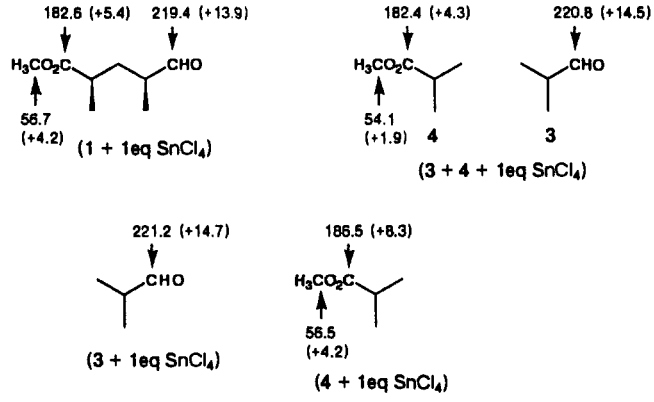


2a (±) Isomer 2b

We previously reported that BF_3-mediated reaction of the meso isomer (**1**) with allyltin gave the anti-Cram erythro adduct predominantly,[3] while the reaction of the (±) isomer (**2**) produced the Cram erythro adduct preferentially.[4] The Cram erythro selectivity of **2** is quite reasonable, since a nonchelation transition state of the Felkin–Anh model[4] is involved. However, the anti-Cram erythro selectivity of **1** requires the intermediacy of a chelation transition state,[3,4] which is improbable because of only one coordination site of BF_3.[5]

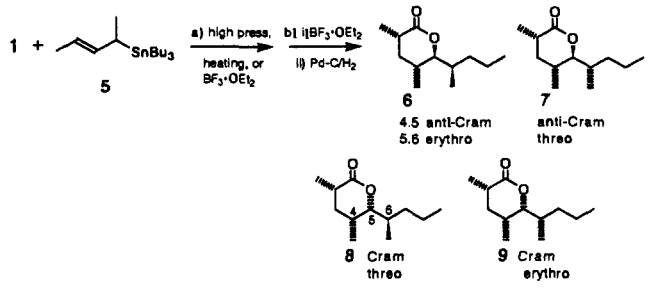
The H_c and H_d protons of **1** appeared at δ ($CDCl_3$) 1.37 and 2.17 ppm, while those of **2** appeared at much closer positions, 1.71 and 1.83 ppm, indicating that the two protons of **1** are under significantly different magnetic circumstances. NOE's were observed at both H_c and H_d of **2** when either H_a or H_b was irradiated. On the other hand, only H_c exhibited an NOE upon irradiation of both H_a and H_b of **1**, indicating that the dihedral angles between H_a and H_d and between H_b and H_d are ca. 180° (supplementary material). Accordingly, the meso isomer presumably adopts stable conformation **1** rather than **1'** because of (i) a significant difference of the chemical shift between H_c and H_d (0.8 ppm) and (ii) the presence of the sterically disfavored pseudo-1,3-diaxial Me groups in **1'**.[6] A rapid equilibrium among **2a**, **2b**, ... exists in the (±) isomer, as an ordinary acyclic molecule.

Scheme I. ^{13}C Chemical Shifts in the Presence of $SnCl_4$[a]



[a] $CDCl_3$; −50 °C; ppm from TMS; (chemical shift difference from the shift without $SnCl_4$).

Scheme II



	product ratio				
	6	7	8	9	anti-Cram/Cram
a) 10 Kbar, 20d, 80°C, CH_2Cl_2	55	26.5	18.5	-	81.5/18.5
a) 150°C, 20h	49	27	24	-	76/24
a) 1eq BF_3·OEt_2	83	7	-	10	90/10

We next examined the ^{13}C NMR spectra to clarify the conformations of **1** and **2** in the presence of Lewis acids. Use of BF_3·OMe_2 produced a trimer of **1** even at −78 °C, which made the spectral analysis difficult.[7] The C-13 chemical shifts in the presence of $SnCl_4$ are shown in Scheme I. The numbers in parentheses designate chemical shift differences between the presence and absence of $SnCl_4$. We used 2-methylpropanal (**3**) and methyl isobutyrate (**4**) as reference compounds. The large shift (+14.5) of CHO and small shifts of CH_3 and CO_2 (+1.9 and +4.3) in the system **3** + **4** + 1 equiv of $SnCl_4$ clearly indicated that $SnCl_4$ selectively coordinated to the aldehyde in the presence of the ester (cf. **3** + 1 equiv of $SnCl_4$, and **4** + 1 equiv of $SnCl_4$). The CH_3 (+4.2) and CO_2 (+5.4) shifts of the system **1** + 1 equiv of $SnCl_4$ revealed that the ester was chelated by $SnCl_4$. This is reasonable, since the two carbonyl groups of **1** are very close and ready to be chelated. Similar experiments with the system **2** + 1 equiv of $SnCl_4$ also indicated the chelation by $SnCl_4$.

Taken together, a stable conformation of **1** must be the same regardless of the presence or absence of $SnCl_4$. Actually, the thermal and high-pressure reaction[8] of **1** with **5** gave the anti-Cram products (**6** and **7**) predominantly (Scheme II). Needless to say, the BF_3-mediated reaction produced the anti-Cram selectivity. The reaction of **1** with crotyltin in the presence of 1 equiv of $SnCl_4$

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(6) The presence of sp^3 Me groups at the diaxial positions is more unfavorable than the presence of sp^2 carbonyl groups.

(7) Such a trimer formation has been observed previously: Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984. Use of $TiCl_4$ caused a very low signal to noise ratio, presumably due to the presence of a radical species. See also: Reissig, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 268.

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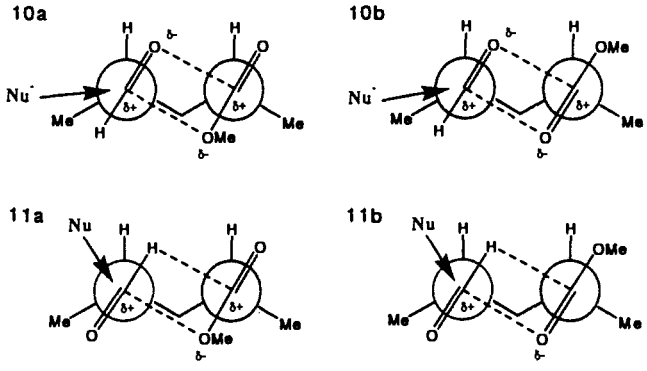
also gave the anti-Cram products with high diastereoselectivity (95/5).

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.

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

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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

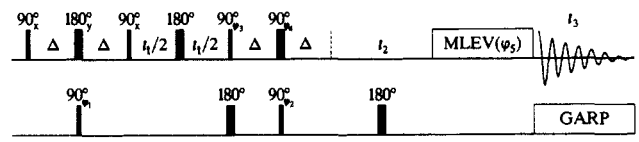

Figure 1. Pulse sequence of the 3D-HQQC-TOCSY spectrum. The delays Δ are set to $(1/2^1J_{CH})$. The following phase cycle is applied: φ_1 = 0, 180, 0, 180; φ_2 = 0, 0, 180, 180; φ_3 = 4 × 0, 4 × 60, 4 × 120, 4 × 180, 4 × 240, 4 × 300; φ_4 = 4 × 90, 4 × 150, 4 × 210, 4 × 270, 4 × 330, 4 × 30; φ_5 = 4 × 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

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