The Structures of E and Z Methyl Octa-6-ene-2,4-Diynoate by Total
Synthesis and NMR

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Os ácidos E e Z-octa-6-eno-2,4-diynicos e seus respectivos ésteres metílicos foram sintetizados
e determinaram-se suas estruturas por métodos espectroscópicos. Os acoplamentos CH a longa
distância, observados nos espectros totalmente acoplados de RMN de $^{13}$C foram particularmente
eucidativos. Foram obtidos cálculos semi-empíricos e ab initio, na tentativa de avaliar as corre-
lações entre cargas atômicas e os deslocamentos químicos observados.

The E and Z isomers of octa-6-ene-2,4-diynoic acid, were synthesized. Their respective methyl
esters were prepared and the structures were determined by spectral data. Long-range CH coupling
observed in $^{13}$C-NMR fully coupled spectra was particularly elucidating. Semiempirical and ab
initio calculations were also carried out in an attempt to evaluate the correlation between atomic
charges and the observed chemical shifts.

Keywords: E and Z Methyl octa-6-ene-2,4-diynoate, $^{13}$C-NMR and semi-empirical and ab
initio calculations

Introduction

We have previously reported the occurrence of (E)
octa-6-ene-2,4-diynoic acid (1) in the roots of Siphocam-
pylus sulfureus (Campanulaceae), the molecular structure
of which was proposed by means of $^{1}$H-NMR (100 MHz)
and mass spectra data. At that time we could not register
the infrared spectrum, while the ultraviolet data were not
consistent with those of the synthetic product prepared by
Jones.

At present, considering that acetylenic acids are usually
fungi metabolites, and noting the rare occurrence of natural
C-8 polyacetylenes, we decided to resynthesize 1 in order
to unambiguously elucidate its molecular structure.

Results and Discussion

Starting from propargyl alcohol (2) we obtained bromo-
propargylic acid (3), which was then condensed with a
mixture of E/Z-penta-3-ene-1-yne (4) [from propargyl bro-
mide and acetaldehyde, via a Reformatzyk reaction, fol-
lowed by tosylation and elimination] through a Cadiot-Chodkiewicz reaction (Scheme 1). After methyla-
tion with methanol acid, followed by chromatography, we
were able to isolate each of the corresponding methyl esters
(5E and 5Z), which were submitted to several NMR experi-
ments (Table 1), including the application of bi-diimen-
sional techniques. We want to emphasize the usefulness of
totally coupled $^{13}$C-NMR spectra for the assignment of C-5
and C-4 chemical shifts in both isomers, taking into account
the characteristic values of the respective long-range cou-
pling constants ($^{2}$JCH and $^{3}$JCH). As such, for the E isomer
(5E) the chemical shifts of C-5 at $\delta$ 82.8 ($^{2}$JCH = 2.1 and
$^{3}$JCH = 7.0 Hz) and C-4 at $\delta$ 70.4 ($^{2}$J = 4.6 Hz) were found.
The broad bands at $\delta$ 70.7 and 71.7 correspond to the
chemical shifts of C-2 and C-3, respectively.
These data are also in agreement with a cis relation of C-5 and H-7 and reinforces the E configuration already shown by the coupling constants of H-6 and H-7 protons (J = 16.0 Hz) in the 1H-NMR spectrum (300 MHz), and by the strong absorption band at 950 cm⁻¹ in the infrared spectrum.

For the Z isomer (5Z), chemical shifts of C-5 at δ 81.0 (\(\delta^1\) /CH = 2.3 and \(\delta^3\) /CH = 14.3 Hz) and C-4 at δ 76.2 (\(\delta^1\) /CH = 4.9 Hz) were found. The singlets at δ 71.4 and 71.8 correspond to the chemical shifts of C-2 and C-3, respectively. These data are also in agreement with a trans relation of C-5 and H-7 and reinforces the Z configuration already shown by the coupling constants of H-6 and H-7 protons (J = 11.0 Hz) in the 1H-NMR spectrum, and by an absorption band at 722 cm⁻¹ in the infrared spectrum.

Although the chemical shifts of C-2 and C-3 are very near in both isomers, we believe that C-2 is more shielded than C-3, based on valence bond theory, considering the resonance hybrids.

Semi-empirical and ab initio calculations were carried out in an attempt to evaluate the agreement between atomic charges and the observed 13C-NMR shifts. All calculations were made using the GAUSSIAN 92 program. The ab initio results were obtained at the Hartree-Fock level of theory with the 6-31G** basis set. The semiempirical calculations were made using the AM1 method from the GAUSSIAN program. Figure 1 shows the fully optimized geometry of the E isomer from both levels of calculation. The results show that no significant discrepancies were observed in the optimized structures, either at the ab initio or semi-empirical (values in parentheses) levels. The larger deviation occurs at the -COO group where the discrepancies between the semi-empirical and ab initio methods are observed.

The AM1 atomic charges were calculated using the Mulliken population at the semi-empirical equilibrium geometry. A test was carried out in which Mulliken charges were also calculated at the ab initio equilibrium geometry, and no significant difference with respect to the atomic charges calculated using AM1 geometry was observed. The ab initio atomic charges were calculated at the respective theoretical equilibrium geometry using four different procedures: a) Mulliken charges, b) charges derived from electrostatic potentials using Kollman's criterion, c) charges calculated from electrostatic potential using the CHELP procedure, and d) the use of electrostatic potential applying the CHELP method. Table 2 shows the calculated charges using these five methods. A reasonable agreement among the atomic charge signals from the four heavier atoms is observed using any of the five methods. However, a comparison between the atomic charges and the 13C-NMR chemical shifts shows that no direct correlation is possible between these two properties. The results for C-1, C-2 and C-3 indicate that, independent of the method used to calculate charges, the high positive charge of C-1 suggests that this is the most unprotected atom of the structure. Its neighbor C-2, having a negative charge presents a more protected nucleus than C-3 and C-5, having positive atomic charges. The atomic charges for these three carbons are in agreement with the 13C-NMR observations. The results for the other heavier atoms show...
Figure 1. The optimized structure calculated at the Hartree-Fock level with the 6-3G** basis set and at the AM1 level of calculation (values in parentheses). Only (a) the bond lengths (in Å) and (b) the bond angles (in degrees) for the planar structure containing the heavier atoms are shown.

Table 2. The atomic charges calculated at the Hartree-Fock level with the 6-31G** basis set, and at the AM1 level at the respective theoretical equilibrium geometries using different methods (see Fig. 1).

<table>
<thead>
<tr>
<th></th>
<th>AM1* Mulliken</th>
<th>6-31G**a (Mulliken)</th>
<th>6-31G**b (MK)</th>
<th>6-31G**c (CHELP)</th>
<th>6-31G**d (CHELP)</th>
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a) Mulliken charges; b) charges derived from the electrostatic potentials using Kollmann's criterion; c) charges derived from the electrostatic potential using the CHELP method; d) charges derived from the electrostatic potential using the CHELPG procedure.
divergence either in the charge signal or in its magnitude and no suggestion for protection can be made with certainty. The reasonable agreement between the atomic charges for the first three carbon atoms and the $^{13}$C-NMR chemical shifts may be associated with the high difference in the electronegativity of the atoms connected to the ester group. The results suggest that the minimization of this effect with atomic distance does not provide a significant separation of the charges, and consequently a possible correlation with $^{13}$C-NMR chemical shifts.

Finally, by comparing the spectral data of the synthetic product ($E$ configuration) with those of the natural product methyl ester, we can now confirm that both have the same configuration.

**Experimental**

UV and IR spectra were obtained in Perkin-Elmer spectrophotometers, Lambda 3A (in CHCl$_3$ solution) and 1600 FTCR series (film, NaCl cells), respectively. NMR data were registered in Bruker ACP-300 equipment ($^1$H at 300 MHz and $^{13}$C at 75.5 MHz). Mass spectra were obtained in a HP GC-MS, model P5970. $E$ and $Z$ methyl ester derivatives were separated by Chromatotron$^{12}$ (elution in CH$_2$Cl$_2$) and purified by continuous PLC$^{12}$ (7 h, run with hexane: AcOEt, 99:1).

($E/Z$) - Pent-3-ene-1-yn (4). Starting from propargyl alcohol, propargyll bromide was prepared and further reacted with acetaldehyde following the procedure described by Whiting et al.$^3$, where (±)-4-pentyn-2-ol was obtained in 44% yield. Spectral data were identical to the literature. After tosylation and heating (135 °C), the mixture of 4 was obtained in a 71% yield: $\nu_{\text{max}}$ (cm$^{-1}$): 3 313 (≡S=H), 2 103 (C≡C), 1 599 and 1 442 (C≡C), 934 (C=C-trans), 812 (C=C-cis).

Bromopropargylic acid (3). Propargyl alcohol was submitted to Jones oxidation and furnished the corresponding acid. Spectral data were identical to the literature. After reaction with NaOBr, bromopropargylic acid was obtained in a 43% yield: $^{13}$C-NMR (CDCl$_3$): δ 156.3 (C-1), 72.2 (C-2) and 55.8 (C-3).

Methyl, ($E/Z$)-octa-6-ene-2,4-diynoate (5)-Cadiot-Chodkiewicz reaction of 3 and 4 according to the procedure by Bohlmann et al.$^4$, followed by methylation (MeOH, H$_2$SO$_4$) furnished the mixtures $E$ and $Z$ of the methyl ester derivatives (5), which were separated by chromatography as mentioned above. $^1$H and $^{13}$C-NMR (Table 1); $E$ isomer: $\nu_{\text{CHCl}}$ (nm) 232, 253, 276, 292 and 340; $\nu_{\text{max}}$ (cm$^{-1}$) 2945, 2221, 1713, 1624, 1436, 1295, 1200, 950; GC-MS[R;R: 20.7 min; m/z (%)] 148 (M$,^+$, 79), 117(100), 105(6), 90(58), 77(35), 63(33), 51(9). $Z$ isomer: $\nu_{\text{CHCl}}$ (nm) 234, 2677, 276, 292, 309, 339; $\nu_{\text{max}}$ (cm$^{-1}$) 2954, 2845, 2220, 1713, 1654, 1438, 1298, 722; GC-MS[Rt19.4 min; m/z (%)] 148 (M$,^+$, 70), 117(100), 105(9), 90(58), 77(35), 63(40), 51(9).

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**References**


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