Tetrahedron Vol. 41, No. 4, pp. 775 to 779, 1985
Printed in Great Britain.

0040–4020/85 $3.00 + .00
Pergamon Press Ltd.

STEREOCHEMICAL ASSIGNMENT BY MASS SPECTROMETRY

DOUBLE BOND GEOMETRICAL ISOMERS OF 3,5-DIALKYLCYCLOHEXYLIDENE ACETIC ACID ESTERS AND 3-ALKYL-2-ALKENOATES

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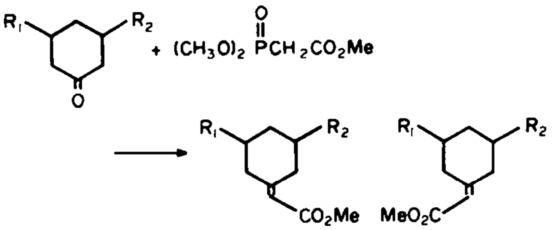
(*Received in UK* 17 *November* 1983)

Abstract—Mass spectrometry is the best physical method for the configurational assignment of *E*- and *Z*-3,5-dialkylcyclohexylidene acetic acid esters **1** and *E*- and *Z*-3-alkyl-2-alkenoates **2**. The homoallylic cleavage resulting in the loss of the C-3 and C-5 alkyl groups from **1** and of the two δ-alkyls from **2** is a stereospecific process: the loss of the group which is adjacent to the carbonyl is significantly preferred. The stereospecificity of this fragmentation is interpreted in terms of a hidden hydrogen transfer preceding the carbon–carbon bond cleavage.

Many examples of different fragmentation patterns of gas phase ions formed from stereoisomeric compounds have been reported.[1-4] These stereochemical effects indicate that mass spectrometry may be used for the determination of configuration in various systems. However this technique has been used for actual configurational assignment in only a limited number of cases.[4-7] We present here a system in which mass spectrometry seems to be the most effective tool for the determination of configuration.

The Wittig reaction between unsymmetrically substituted 3,5-dialkylcyclohexanones and methyl dimethylphosphonoacetate gave rise to the esters of the corresponding *Z*- and *E*-cyclohexylidene acetic acids **1**. Gas chromatographic analysis indicated the formation of only two isomers in a 1 : 1 ratio in each of



Z-1 *E*-1

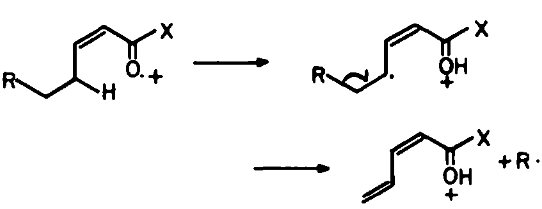
$R_1 = CH_3$; $R_2 = C_2H_5$
$R_1 = CH_3$, $R_2 = n\text{-}C_3H_7$
$R_1 = CH_3$ $R_2 = 2\text{-}C_3H_7$

Table 1. Abundance of $[M-R]^+$ ions in the mass spectra of methyl *Z*- and *E*-3,5-dialkylcyclohexylidine acetates **1**

	R_1	R_2	$[M-R_1]^+/M^{+\cdot}$	$[M-R_2]/M^{+\cdot}$	$[M-R_2]^+/[M-R_1]^+$	Z/E
Z-1a	CH_3	C_2H_5	0.16	4.8	30	17
E-1a	"	"	0.77	1.4	1.8	
Z-1b	CH_3	$n\text{-}C_3H_7$	0.50	12	24	5
E-1b	"	"	0.94	4.4	4.7	
Z-1c	CH_3	$2\text{-}C_3H_7$	0.14	29	207	36
E-1c	CH_3	"	1.03	6.0	5.8	

the three cases studied. We assume that the two alkyl groups at C-3 and C-5 attain the more stable *cis*-configuration, and the difference between the isomers lies in the geometry of the double bond.

A significant difference between the mass spectra of the isomers *Z*-**1** and *E*-**1** was observed in the abundance of $[M-R]^+$ ions formed by the loss of one of the substituents at positions 3 and 5 (Table 1). A homoallylic cleavage in α,β-unsaturated carbonyl compounds has been shown to occur by a two-step mechanism (Scheme 1) which involves a "hidden hydrogen transfer" from an allylic position to the carbonyl oxygen atom.[8] This fragmentation shows a significant specificity to *cis*-configuration of the double bond in the case of *cis*- and *trans*-octadec-2-enoates.[8a]

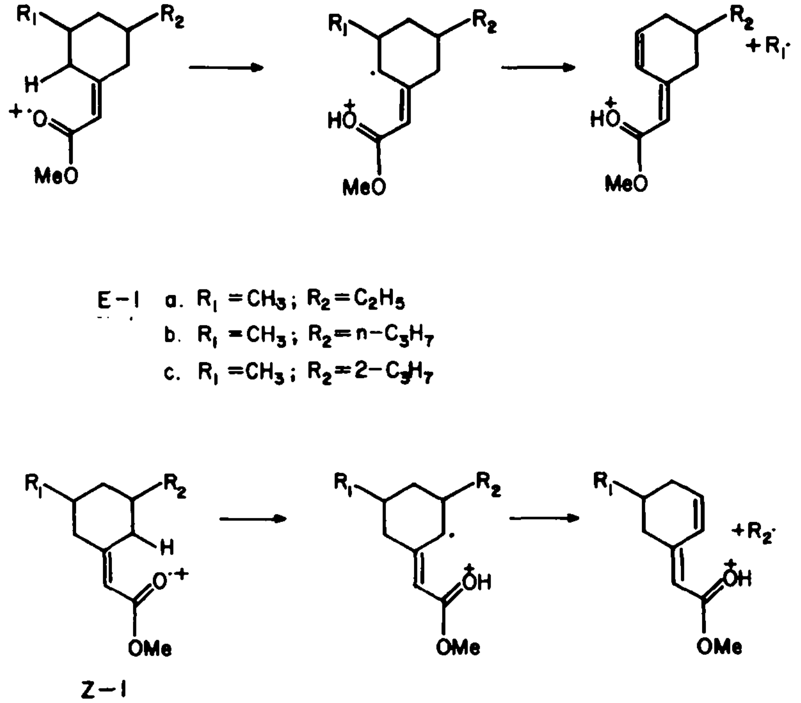


Scheme 1.

The different mass spectra of the isomers *Z*-**1** and *E*-**1** indicate that the geometry of the double bond is retained to a great extent under electron impact ionization. The difference in the abundance of the $[M-R]^+$ ions can be explained by a similar two-step fragmentation initiated by the migration of an allylic hydrogen atom adjacent to the carbonyl oxygen in the specific stereoisomer (Scheme 2). Thus mass spectrometry can be used as a tool in the assignment of configuration of 3,5-dialkylcyclohexylidene acetic acid esters. Greater relative abundance of an $[M-R]^+$ ion formed by the loss of one of the two alkyl substituents indicates the adjacency of that alkyl group to the carbonyl group. This relationship has been previously used in the determination of configuration of *Z*- and *E*-3-methyl-4-ethylcyclopentylidene acetic acid esters.[4] The present results are an indication of the generality of the method.

Mass spectrometry was also applied in the configurational assignment of the isomeric methyl *E*- and *Z*-3-methylcyclohexylidene acetates. Because of the lack of a substituent at C-5 the ion abundance ratio $[M-CH_3]^+/[M^{+\cdot}]$ was used for the assignment in this case. This ratio was 2.9 for the *Z*- and 1.5 for the *E*-isomer.

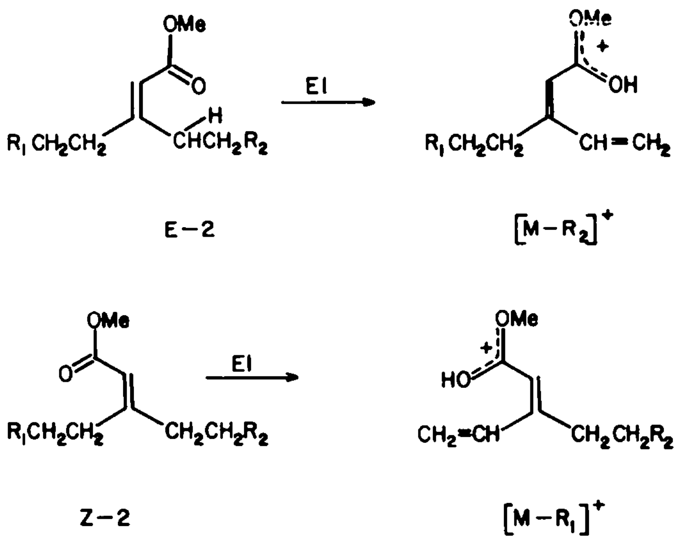
The comparison of the abundances of ions formed by the homoallylic cleavage can be also used for the determination of the double-bond geometry in *Z*- and *E*-3-alkyl-2-alkenoates **2**. These pairs of geometrical isomers were synthesized by a similar route, namely Wittig reaction of various aliphatic ketones with methyl dimethylphosphonoacetate. The abundance data of the $[M-R]^+$ ions obtained by the two competing homoallylic cleavages are listed in Table 2. Here again the loss of the alkyl group adjacent to the carbonyl is preferred, though to a smaller extent than in **1**. These data indicate the occurrence of a partial isomerization in *Z*-**2** and *E*-**2** on ionization, but the comparison of abundances can undoubtedly be used for the configurational assignment.



E-1 a. $R_1 = CH_3$; $R_2 = C_2H_5$
b. $R_1 = CH_3$; $R_2 = n\text{-}C_3H_7$
c. $R_1 = CH_3$; $R_2 = 2\text{-}C_3H_7$

Z-1

Scheme 2.



E-2

$[M-R_2]^+$

Z-2

$[M-R_1]^+$

It should be emphasized that other physical techniques (IR, UV and nmr spectroscopy) are insensitive to configurational differences in these systems, and mass spectrometry is the best and simplest technique for the determination of configuration. The assignment may be conveniently achieved on the mixture of isomers with the combination of gas chromatography and mass spectrometry (GC–MS). Here the configurational assignment can be made by monitoring of the abundance of the two relevant $[M-R]^+$ ions formed by the competing homoallylic cleavage processes as a function of time. The result of such an analysis is shown in Figs. 1 and 2.

EXPERIMENTAL

Mass spectra were measured with a Varian MAT 711 double focusing spectromometer. GC–MS measurements were performed on a Finnigan 4021 mass spectrometer. The separation was performed on a 30 m capillary column coated with SE54.

3,5-Dialkyl-Δ^2-cyclohexenones were prepared by the reaction of ethyl acetoacetate and the corresponding aldehydes.[9–11]

3,5-Dialkylcyclohexanones were obtained by hydrogenation of the corresponding 3,5-dialkyl-Δ^2-cyclohexenones on 5% Pd/C in absolute ethanol at 40 psi. 3-Methyl-5-ethylcyclohexanone: Bp_{25} 109–110° (lit.[11] Bp_{760} 215°). 3-Methyl-5-isopropylcyclohexanone: Bp_{25} 118–120° (lit.[12] Bp_{760} 225°). 3-Methyl-5-propylcyclohexanone: Bp_{25} 115–7°.

The alkanones used for the synthesis of **2** were prepared by the reaction of acyl chlorides with the corresponding organocadmium reagents.[13] 4-Nonanone: prepared from butanoyl chloride and di-n-pentylcadmium (65%). Bp_{20} 91–2° (lit.[14] $Bp_{25\,5}$ 88.8–8.89°). 5-Undecanone: prepared from heptanoyl chloride and di-n-butylcadmium (55%). Bp_{25} 120° (lit.[15] Bp_{11} 104–6°). 6-Dodecanone: prepared from heptanoyl chloride and di-n-pentylcadmium (60%). Bp_{25} 125° (lit.[16] Bp_9 112°). 5-Dodecanone: prepared from octanoyl chloride and di-n-butylcadmium (60%). Bp_{25} 126° (lit.[17]

Table 2. Abundance of $[M-R]^+$ ions in the mass spectra of methyl *Z*- and *E*-3-alkyl-2-alkenoates **2**

	R_1	R_2	$[M-R_1]^+/M^+$	$[M-R_2]^+/M^+$	$[M-R_2]^+/[M-R_1]^+$	Z/E
Z-1a	CH_3	$n\text{-}C_4H_9$	0.13	3	23	1.3
E-2a	"	"	0.16	2.8	18	
Z-2b	C_2H_5	$n\text{-}C_4H_9$	0.74	7.2	9.7	5.1
E-2b	"	"	1.6	3.1	1.9	
Z-2c	C_2H_5	$n\text{-}C_5H_{11}$	0.6	4.4	7.3	7.3
E-2c	"	"	1.5	1.5	1	
Z-2d	$n\text{-}C_3H_7$	$n\text{-}C_4H_9$	0.6	2.5	4.2	7
E-2d	"	"	1.7	1.1	0.6	
Z-2e	$n\text{-}C_3H_7$	$n\text{-}C_5H_{11}$	0.46	5.8	13	5.9
E-2e	"	"	1.5	3.3	2.2	

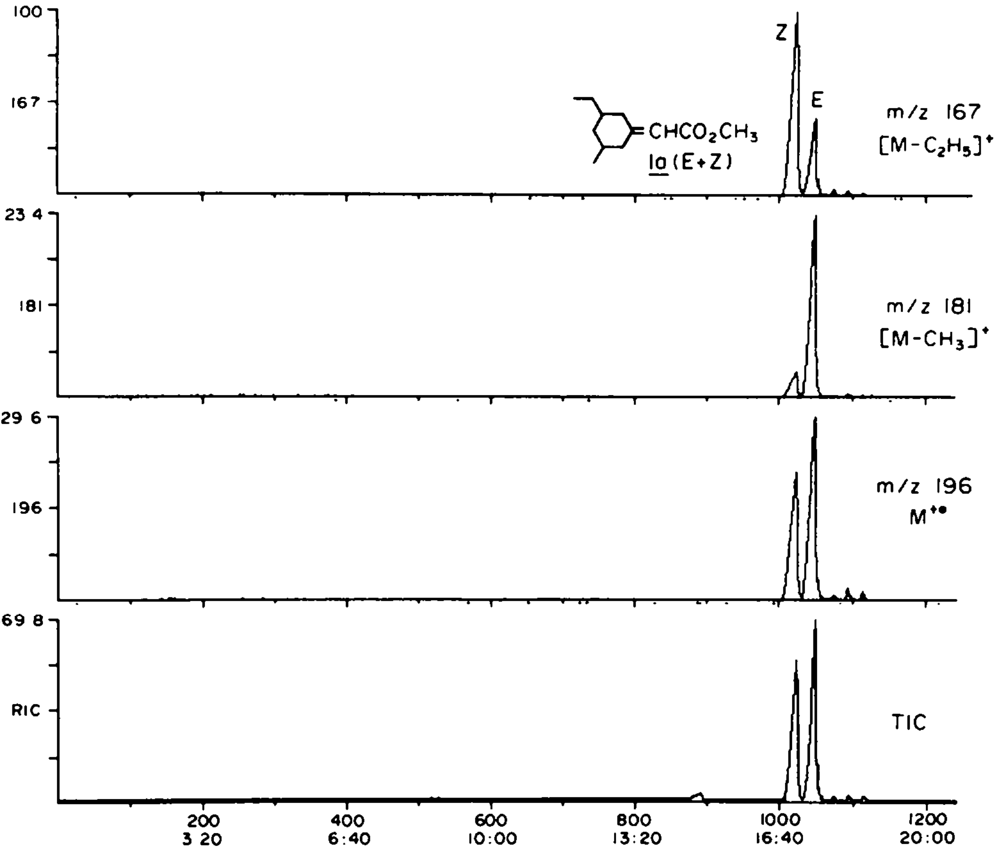


Fig. 1. GC–MS analysis of methyl *E*- and *Z*-3-methyl-5-ethylcyclohexylidene acetates (**1a**-*E* and **1a**-*Z*).

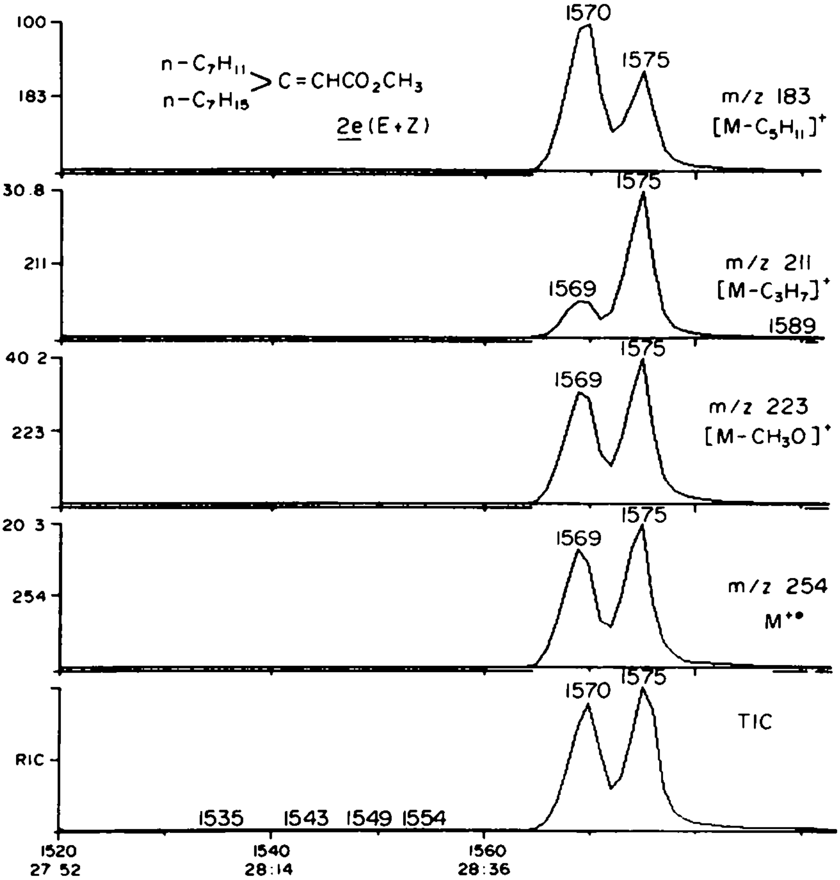


Fig. 2. GC–MS analysis of methyl *E*- and *Z*-3-pentyl-2-decenoates (**2e**-*E* and **2e**-*Z*).

Bp$_9$ 119°). 6-Tridecanone: prepared from octanoyl chloride and di-n-pentylcadmium (65%). Bp$_{25}$ 132° (lit.[15] Bp$_4$ 110–3°).

The α,β-unsaturated esters **1** and **2** were prepared by Wittig reaction of the corresponding dialkylcyclohexanones and alkanones with methyl dimethylphosphonoacetate.[18] The double bond geometrical isomers *E*- and *Z*-methyl 3,5-dialkylcyclohexylidene acetates **1** were separated by gas chromatography on a 4 m column of 15% Carbowax on Chromosorb Q. The separation of the geometrical isomers of the 3-alkyl-2-alkenoates **2** was achieved by capillary gas chromatography using a 30 m SE 54 coated column.

Methyl 3-methyl-5-ethylcyclohexylidene acetate **1a** (*E* + *Z* mixture): 75% yield. Bp$_{25}$ 136–8°. Methyl 3-methyl-5-propylcyclohexylidene acetate **1b** (*E* + *Z* mixture): 75% yield. Bp$_{25}$ 160–2°. Methyl 3-methyl-5-isopropylcyclohexylidene acetate **1c** (*E* + *Z* mixture): 75% yield. Bp$_{25}$ 158–160°. Methyl 3-methylcyclohexylidene acetate **1d** (*E* + *Z* mixture): 70% yield. Bp$_{25}$ 126–8°. Methyl-3-propyl-2-nonenoate **2a** (*E* + *Z* mixture): 30% yield. Bp$_{25}$ 126–8°. Methyl-3-butyl-2-nonenoate **2b** (*E* + *Z* mixture): 35% yield. Bp$_{25}$ 140–2°. Methyl-3-butyl-2-decenoate **2c** (*E* + *Z* mixture): 30%. Bp$_{25}$ 142–5°. Methyl-3-pentyl-2-nonenoate **2d** (*E* + *Z* mixture): 25%. Bp$_{25}$ 142–5°. Methyl-3-pentyl-2-decenoate **2e** (*E* + *Z* mixture): 30%. Bp$_{25}$ 148–150°.

Acknowledgement—We are grateful to Dr. A. Tishbee from the Weizmann Institute for the GC-MS analyses. This work was supported by the Fund for Promotion of Research at the Technion.

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