ORGANIC MASS SPECTROMETRY, VOL. 29, 342–346 (1994)

Mechanism of Stereospecific Alcohol Elimination from Cyclohexane *trans*-1,3-Dicarboxylates Under Electron Impact Ionization

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Diesters of cyclohexane *trans*-1,3-dicarboxylic acid give rise to major $[M - ROH]^{+\cdot}$ ions under electron impact ionization. A mass spectral study of the isomeric mixed methyl ethyl esters of the diacid, substituted by a methyl group at position 1 and deuterium labelled at position 3, indicates a stepwise mechanism for this alcohol elimination; the 3-hydrogen (or deuterium) is transferred to the carbonyl of the 1-ester group in the initial step. Subsequent migration of that hydrogen (or deuterium) to the alkoxyl of position 3 results in the highly site- and stereospecific alcohol elimination. CID spectra of the $[M - ROH]^{+\cdot}$ ions obtained from the stereoisomeric diesters clearly show that they have different structures (or are different mixtures of structures).

INTRODUCTION

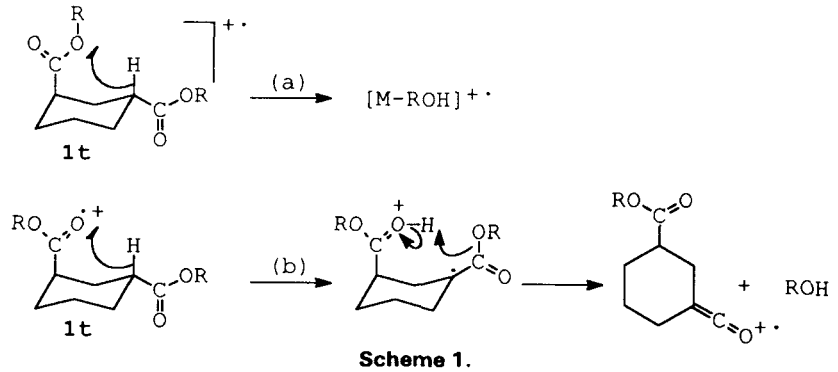
The effect of configuration on the fragmentation pattern of esters of various stereoisomeric dicarboxylic acids under electron impact (EI) ionization has been described in several reports.[1–4] We have previously reported a stereospecific elimination of methanol from dimethyl cyclohexane *trans*-1,3-dicarboxylate (**1t**) under EI ionization.[1–3] The epimeric *cis*-diester **1c** undergoes a preferential loss of an alkoxy radical. A deuterium-labelling study indicated involvement of one of the α-hydrogen atoms (from position 1 or 3) in the above elimination of alcohol from the *trans*-diester.[3] A plausible mechanism proposed for this elimination is shown in Scheme 1 [route (a)]. A 1,4-transfer of the axial hydrogen from position 1 to the alkoxy oxygen of the 3-alkoxycarbonyl group has been suggested to lead directly to the $[M - ROH]^{+\cdot}$ ion.[2,3] Analogous hydrogen transfers from activated positions (α to carbonyl, allylic) to alkoxy oxygen atoms of ester groups have also been proposed as the mechanistic pathways of the stereospecific formation of $[M - ROH]^{+\cdot}$ ions in several other diester systems.[1–4]

There is another, more complex, route that could be suggested as the pathway to the formation of $[M - ROH]^{+\cdot}$ ions from the above diesters. This possible pathway is shown in route (b) in Scheme 1 of cyclohexane *trans*-1,3-dicarboxylates. It consists for two rearrangement steps: (i) transfer of an axial α-hydrogen from position 1 to the carbonyl oxygen of the axial 3-alkoxycarbonyl group and (ii) migration of that hydrogen from the carbonyl of position 3 to the alkoxyl of position 1 followed by alcohol elimination. In this paper, we present compelling evidence for the occurrence of route (b).

RESULTS AND DISCUSSION

α-Methylation and deuterium-labelling study

The two isomeric mixed methyl ethyl diesters of 1-methylcyclohexane *trans*-1,3-dicarboxylic acid, **2t** and **3t**, and their analogues **2t-*d***, and **3t-*d*** substituted by deuterium and position 3, were prepared and their EI mass spectra measured, in order to differentiate between the two possible mechanistic pathways of formation of the $[M - ROH]^{+\cdot}$ ions under EI ionization shown in Scheme 1. The 70 eV EI mass spectral data for **2t** and **3t**



Scheme 1.

CCC 0030–493X/94/070342–05

Received 7 January 1994
Revised 25 February 1994
Accepted 8 March 1994

Table 1. 70 eV EI mass spectral data for isomeric methylethyl esters of stereoisomeric 1-methyl cyclohexane 1,3-dicarboxylic acids

		Relate abundance (%)[a]			
m/z	Ion	**2t**	**3t**	**2c**	**3c**
197	$[M - MeO]^+$	9[b]		2[b]	4[b]
196	$[M - MeOH]^{+\cdot}$	34		9	13
183	$[M - EtO]^+$	5[b]	12[b]	5[b]	
182	$[M - EtOH]^{+\cdot}$	7	49	5	5
170		4	3	2	8
169	$[M - COOMe]^+$	13[b]	12	10[b]	36[b]
168	$[M\text{-}MeOH - CO]^{+\cdot}$	50	5	23	10
156		10	3	15	3
155	$[M - COOEt]^+$	24[b]	14[b]	38[b]	11[b]
154	$[M - EtOH - CO]^{+\cdot}$	12	43	14	13
141		3		9	
140		7	2	6	
124		9	3	16	10
123		23	16	42	12
122		15	21	10	7
115		4		2	
114		3			
97		3	5	4	4
96		33	20	37	56
95	$[M - 2COOR - H]^+$	100	100	100	100
94		17	17	11	9
93		5	5	3	7
91					2
81		8	6	7	4
69			5	2	4
67		8	8	7	12
59			2		18

[a] Relative abundances below 2% not listed.
[b] Not corrected for ^{13}C isotope contribution.

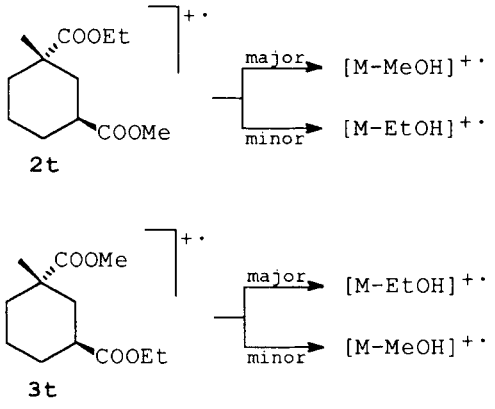
Table 2. 70 eV EI mass spectral data for isomeric methyl ethyl esters of stereoisomeric 3-deuterated 1-methylcyclohexane 1,3-dicarboxylic acids

		Relative abundance (%)[a]			
m/z	Ion	**2t-d_1**	**3t-d_1**	**2c-d_1**	**3c-d_1**
198	$[M - MeO]^+$	9[b]		2[b]	3[b]
197	$[M - MeOH]^{+\cdot}$	16[b,c]	4	7	9
196	$[M - MeOD]^{+\cdot}$	48			
184	$[M - EtO]^+$	4[b]	18[b]	8[b]	2[b]
183	$[M - EtOH]^{+\cdot}$	13[d]	18[b,d]	16[d]	8
182	$[M - EtOD]^{+\cdot}$		96	2	
171					4
170	$[M - COOMe]^+$	15[b]	25[b]	9[b]	40
169	$[M - MeOH - CO]^{+\cdot}$	16[b,e]	9[b,e]	9[e]	8[b,e]
168	$[M - MeOD - CO]^{+\cdot}$	66	7	2	7
157		4		6	
156	$[M - COOEt]^+$	37[b]	23[b]	53[b]	8[b]
155	$[M - EtOH - CO]^{+\cdot}$	22[f]	20[b,f]	27[f]	15[f]
154	$[M - EtOD - CO]^{+\cdot}$	7	64	3	3
141		10		5	3
140		3			3
125		4	3	5	2
124		31	25	48	16
123		15	9	15	7
122		13	22		2
115		7		2	
97		10	11	10	12
96	$[M - 2COOR - H]^+$	100	100	100	100
95		56	38	20	30
94		15	17	3	10

[a] Relative abundances below 2% not listed.
[b] Not corrected for ^{13}C isotope contribution.
[c] Not corrected for the contribution of $[M(d_0) - MeO]^+$.
[d] Not corrected for the contribution of $[M(d_0) - EtO]^+$.
[e] Not corrected for the contribution of $[M(d_0) - COOMe]^+$.
[f] Not corrected for the contribution of $[M(d_0) - COOEt]^+$.

are given in Table 1 and those of **2t**-*d*, and **3t**-*d*, in Table 2.

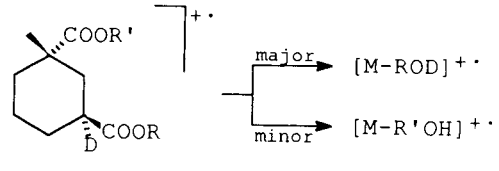
The mass spectra of **2t** and **3t** show clear preference for the elimination of an alcohol originating from the unsubstituted ester group of position 3 (Scheme 2). The *m/z* 196 $[M - MeOH]^{+\cdot}$ ion is much more abundant than the *m/z* 182 $[M - EtOH]^{+\cdot}$ counterpart in the mass spectrum of **2t** (34% vs 7%), and the latter is accompanied by a comparable *m/z* 183 $[M - EtO]^+$ (5%) ion. An even more pronounced preference was observed in the case of **3t**: the *m/z* 182 $[M - EtOH]^{+\cdot}$ ion is highly abundant (49%), whereas $[M - MeOH]^{+\cdot}$ is negligible (*m/z* 196, <0.5%).



Scheme 2.

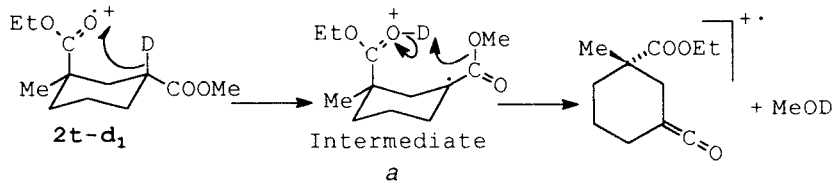
The mass spectra of the deuterium-labelled analogues **2t**-d_1, and **3t**-d_1 (Table 2) demonstrate abstraction of the deuterium atom from position 3 in the course of elimination of the alcohol molecule originating at the alkoxycarboxyl group from the same position 3 (see Scheme 3). This 3-hydrogen atom is not abstracted in the course of formation of the low-abundance $[M - ROH]^{+\cdot}$ ions involving the other alkoxyl from the ester group of position 1.

The epimeric *cis*-diesters **2c** and **3c** exhibit relatively low-abundance $[M - ROH]^{+\cdot}$ ions (*m/z* 196 $[M - MeOH]^{+\cdot}$ and *m/z* 182 $[M - EtOH]^{+\cdot}$, 9% and 5% for **2c**, 13% and 5% for **3c**; see Table 1). The mass spectra of the deuterium-labelled analogues **2c**-d_1 and



2t-d_1: R=Me; R'=Et
3t-d_1: R=Et; R'=Me

Scheme 3.



Scheme 4.

Table 3. CID[a] mass spectral data for $[M - MeOH]^{+\cdot}$ ions obtained from *trans*- and *cis*-diesters 2t and 2c

		Relative abundance (%)[b]	
m/z	Ion	2t	2c
196	Precursor	423	664
195			13
168	$[P - CO]^{+\cdot}$	100	100
154		2	14
150		2	25
149			5
141			6
140		3	3
139		2	2
122	$[P - CO - EtOH]^{+\cdot}$	15	36
96		1	24
95		75	32
94		14	18
93			2
88			4
82			3
81			12
80			8

[a] 30 eV collision energy.
[b] Abundances below 2% not listed.

Table 4. CID[a] mass spectral data for $[M - EtOH]^{+\cdot}$ ions obtained from *trans*- and *cis*-diesters 3t and 3c

		Relative abundance (%)	
m/z	Ion	3t	3c
182	P (precursor)	561	777
181			8
180			4
179			3
164	$[P - H_2O]^{+\cdot}$		8
154	$[P - CO]^{+\cdot}$	100	100
150	$[P - MeOH]^{+\cdot}$		18
140			15
138			3
127			3
123			3
122	$[P - MeOH - CO]^{+\cdot}$	33	44
108			3
96			9
95		99	58
94		23	30
82			3
81			10
80			11
79		2	
69		3	

[a] 30 eV collision energy.
[b] Abundances below 2% not listed.

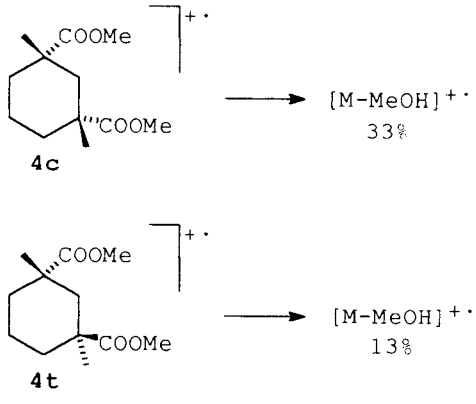
3c-d_1 (Table 2) show that the α-hydrogen atom from position 3 is not involved in the elimination of any of the two alcohols from positions 1 and 3 in the *cis*-diesters.

The above findings indicate that the ester group of position 1 plays a role in the elimination of the alcohol molecule involving both the alkoxyl and the hydrogen from C-3 in the *trans*-diesters. These results suggest the occurrence of a hydrogen transfer from C-3 to the carbonyl at position 1 (intermediate *a*), followed by migration of that hydrogen to the alkoxyl of position 3

Table 5. CID[a] mass spectral data for $[M - EtOH]^{+\cdot}$ ions obtained from the unsubstituted *trans*- and *cis*-diethyl esters 1t and 1c

		Relative abundance (%)[b]	
m/z	Ion	1t	1c
182	Precursor	526	815
181			12
180			7
154	$[P - CO]^{+\cdot}$	100	100
153			4
140		10	
136	$[P - EtOH]^{+\cdot}$	5	28
126		3	5
125		3	5
109			3
108	$[M - CO - EtOH]^{+\cdot}$	21	24
82		5	28
81		39	38
80		22	17
67			5

[a] 30 eV collision energy.
[b] Abundances below 2% not listed.



Scheme 5.

Table 6. 70 eV EI mass spectral data for dimethyl esters of 1,3-dimethylcyclohexane *cis*- and *trans*-1,3-dicarboxylic acids

		Relative abundance (%)[a]	
m/z	Ion	**4c**	**4t**
197	$[M - MeO]^+$	8[b]	3[b]
196	$[M - MeOH]^{+\cdot}$	33	13
181		3	
170		2	5
169	$[M - COOMe]^+$	22[b]	47[b]
168	$[M - MeOH - CO]^{+\cdot}$	41	12
159			8
154		7	4
137		5	10
136		6	3
128		7	
113		2	
110		14	12
109	$[M - 2COOR - H]^+$	100	100
108		15	3
107		8	3
95		27	15
94		3	4
93		13	7
91		6	5
81		11	7
79		6	4
77		9	7
67		11	11
59		32	31

[a] Relative abundances below 2% not listed.
[b] Not corrected for ^{13}C isotope contribution.

resulting in the alcohol elimination. This sequence, shown in Scheme 4, is consistent with route (b) of Scheme 1.

It is interesting to note that the above results, summarized in Scheme 4, indicate non-occurrence of a proton transfer between the two carbonyls at C-1 and C-3 in intermediate *a* on the time-scale of the mass spectral measurement. Such a transfer would result elimination of alcohol involving the alkoxyl from the 1-ester group and the α-hydrogen from position 3.

CID measurements

The results of collision-induced dissociation (CID) measurements of the *m/z* 196 $[M - MeOH]^{+\cdot}$ and *m/z* 182 $[M - EtOH]^{+\cdot}$ ions, obtained under EI from **2t**, **2c**, **3t** and **3c**, are given in Tables 3 and 4.

The unsubstituted cyclohexane 1,3-dicarboxylates exhibit a similar stereospecific behaviour: The different CID mass spectra of the $[M - ROH]^{+\cdot}$ ions obtained from the *cis* and *trans* isomers (Table 5) indicate different structures for these ions.

1,3-Dimethylcyclohexane 1,3-dicarboxylates

The mass spectral data of the dimethyl esters of 1,3-dimethylcyclohexane *cis*- and *trans*-1,3-dicarboxylic acids, **4c** and **4t**, are given in Table 6. The mass spectra are significantly different, permitting easy distinction between the stereoisomers. The *cis* isomer exhibits preferential elimination of methanol and subsequent loss of CO to afford abundant *m/z* 196 and 168 ions, respectively (Scheme 5). It may be assumed that in the absence of a hydrogen at an α-position of a carbonyl, one of the ring or methyl hydrogen atoms is abstracted by a carbonyl group. The subsequent transfer of that hydrogen to the methoxyl of the other ester group, resulting in methanol elimination, is possible only in the *cis*-diester **4c**, if no rearrangement is involved. This may explain the relatively lower abundance of the $[M - MeOH]^{+\cdot}$ ion in the mass spectrum of **4t** and the relatively high abundance of the *m/z* 169 $[M - COOMe]^+$ ion. The preferential elimination of methanol from **4c** resembles in this respect the stereospecific alcohol elimination from MH^+ ions of diesters on chemical ionization.[6,7]

CONCLUSION

The results obtained show that the stereospecific EI-induced alcohol elimination from diesters of cyclohexane *trans*-1,3-dicarboxylic acid and of its α-methyl-substituted analogue is a stepwise process involving a 'hidden hydrogen transfer.' In the initial step an axial α-hydrogen is transferred to the carbonyl of the remote axial ester group, and a subsequent migration of the latter hydrogen to the alkoxyl of the other ester group results in the alcohol elimination. The stepwise nature of alcohol elimination has been proposed previously for cyclohexane *trans*-1,4-dicarboxylates.[1–3] This double hydrogen transfer should also be considered as a possible mechanistic pathway in analogous elimination processes in other systems.

EXPERIMENTAL

Mass Spectrometry

Gas chromatographic/EI and CI mass spectrometric (GC/MS) measurements were carried out on a Finnigan TSQ-70B triple-stage quadrupole mass spectrometer. The separations were performed on a DB-5 (0.25 μm film thickness) capillary column (30 m × 0.25 mm i.d.). The column temperature was programmed from 80 to 180 °C at 4 °C min^{-1}. The scan rate was 0.5 s^{-1}. EI measurements were performed at ion source temperature 150 °C and electron energy 70 eV. Isobutane CI measurements were performed at ion source temperature 150 °C and reagent gas pressure (indicated) 0.4 Torr (1 Torr = 133.3 Pa). CID measurements were performed with argon as the target gas [0.3 mTorr (indicated) at 30 eV collision energy (indicated). All data presented in the tables were obtained on a single day under identical conditions in order to ensure reliable comparisons.

Materials

Mixtures of dimethyl and diethyl esters of 1-methylcyclohexane *cis*- and *trans*-1,3-dicarboxylic acids

and of 1,3-dimethylcyclohexane *cis*- and *trans*-1,3-dicarboxylic acids were prepared by α-methylation of the corresponding esters of cyclohexane 1,3-dicarboxylic acid (commercial mixtures of stereo isomers **1c** and **1t**) with iodomethane and lithium diisopropylamide (LDA) in tetrahydrofuran.[5,6] The mixture contained also the corresponding dimethyl or diethyl esters of 1,3-dimethylcyclohexane *cis*- and *trans*-1,3-dicarboxylic acids (**4c** and **4t**) (products of disubstitution).

The mixture of 1-ethyl-3-methyl esters of 1-methylcyclohexane *cis*- and *trans*-1,3-dicarboxylic acids (**2c** and **2t**, respectively) was prepared by *trans*-esterification of the above mixture of the diethyl esters of 1-methylcyclohexane *cis*- and *trans*-1,3-dicarboxylic acids with methanol. This was achieved by quenching the α-methylation reaction of the diethylcyclohexane 1,3-dicarboxylate (*cis* and *trans* isomers) with methanol (2 h at ambient temperature). Only the unsubstituted 3-ester group undergoes *trans*-esterification under these conditions. The isomeric 1-methyl-3-ethyl esters of 1-methylcyclohexane *cis*- and *trans*-1,3-dicarboxylic acids (**3c** and **3t**) were prepared analogously by *trans*-esterification of the corresponding dimethyl ester with ethanol. The mixtures of products of the *trans*-esterification reactions were submitted to GC/MS analysis. The elution sequences were **1t** (dimethyl ester) followed by **1c** (dimethyl ester), **2t**, **4c** (diethyl ester), **2c** and **4t** (diethyl ester) for the methanol *trans*-esterification and **4c** (dimethyl ester) followed by **4t** (dimethyl ester), **3t**, **3c**, **1t** (diethyl ester) and **1c** (diethyl ester) for the ethanol *trans*-esterification.

Structural and configurational assignments were made with the aid of EI and ammonia CI mass spectrometry.[6] The extent of α-substitution was determined by the *m/z* values of the most abundant $[M - 2ROH - H]^+$ ions in the 70 eV EI mass spectra: *m/z* 81 for the unsubstituted esters **1**, *m/z* 95 for the monosubstituted analogues **2** and **3** and *m/z* 109 for the disubstituted analogue **4**. The *cis*-diesters exhibited major MH^+ ions in the ammonia CI mass spectra, whereas the *trans* isomers gave rise to major attachment ions $[M + NH_4]^+$.[6]

The deuterium-labelled analogs were prepared by quenching the LDA-catalyzed α-methylation reaction with MeOD or EtOD instead of unlabelled methanol or ethanol. Partial separation of deuterated and non-deuterated esters was achieved by GC: the deuterium-labelled material preceded the non-deuterated material. In the absence of molecular ions in the mass spectra, the isotopic enrichment was roughly estimated from the abundances of the *m/z* 95 and 96 ions corresponding to the formal loss of the two ester groups and one hydrogen atom. The concentration of the deuterium-labelled analogues was about (probably higher than) 75% for **2t**-d_1, 85% for **3t**-d_1, 90% for **2c**-d_1, and 85% for **3c**-d_1.

Acknowledgements

This work was supported by the Centre for Absorption in Science, Ministry of Immigrant Absorption, and by the Fund for Promotion of Research at the Technion.

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