ORGANIC MASS SPECTROMETRY, VOL. 28, 230–234 (1993)

Mechanism of Electron Impact Ionization-induced Halogen Elimination From 2-Methyl-2-bromosuccinates†

D. Bornstein, A. Mandelbaum* and I. Vidavsky
Department of Chemistry, Technion—Israel Institute of Technology, Haifa, Israel

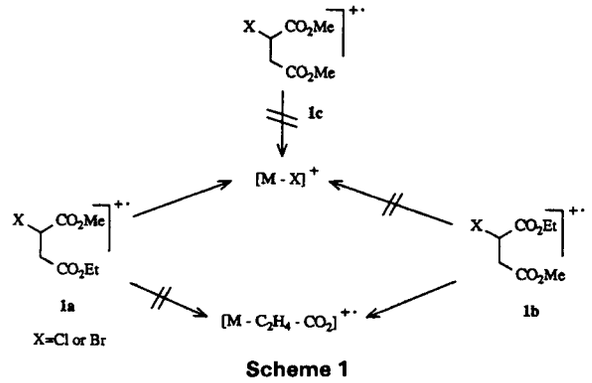
B. Domon, D. R. Mueller and W. J. Richter*
Central Research Services, Ciba-Geigy AG, CH-4002 Basle, Switzerland

The electron impact-induced halogen elimination from 2-methyl-2-bromosuccinates occurs only in the one of the two isomeric methyl ethyl esters in which the ethoxycarbonyl group is remote from the halogen, in analogy with the corresponding previously reported halosuccinates. However, the occurrence of debromination in dimethyl 2-methyl-2-bromosuccinate contrasts with the behaviour of dimethyl bromosuccinate, indicating different mechanisms for this process in the two systems. Collision-induced dissociation (CID) and deuterium labelling studies led to the conclusion that a hydrogen transfer from the 2-methyl group to a carbonyl precedes the elimination of Br˙ from dimethyl 2-methyl-2-bromosuccinate, resulting in a protonated dimethyl itaconate structure for the $[M - Br]^+$ ion. An analogous process is the major route leading to $[M - Br]^+$ ion from 1-methyl-4-ethyl 2-methyl-2-bromosuccinate. In this case deuterium labelling and CID measurements indicated a significant contribution of methyl ethyl citraconate and possibly mesaconate owing to partial operation of a mechanism similar to that reported for 1-methyl-4-ethyl 2-bromosuccinate.

INTRODUCTION

In a previous paper[1] we showed that the electron impact-induced elimination of a halogen atom from chloro- and bromosuccinates is a highly specific process: it takes place in one of the two isomeric methyl ethyl esters in which the halogen is remote from the ethoxycarbonyl group (**1a**), but not in the other isomer **1b** or in dimethyl halosuccinates **1c** (see Scheme 1). Another highly specific fragmentation is the sequential elimination of C_2H_4 and CO_2, which occurs in **1b** but not in the isomeric **1a** (see Scheme 1).[1]

A low-energy collision-induced dissociation (CID) investigation of specifically deuterium-labelled analogues of **1a** suggested a protonated maleate (major) and fumarate (minor) structure for the $[M - X]^+$ ion and a multi-step mechanism for their formation (Scheme 2). The final hydrogen migration step in the suggested mechanism involves one of the two hydrogen atoms from position 3 of the succinic moiety. We turned to the study of analogous isomeric 2-methyl-2-bromosuccinates **2** in order to investigate the generality of the above process. The results of that investigation are the subject of this paper.

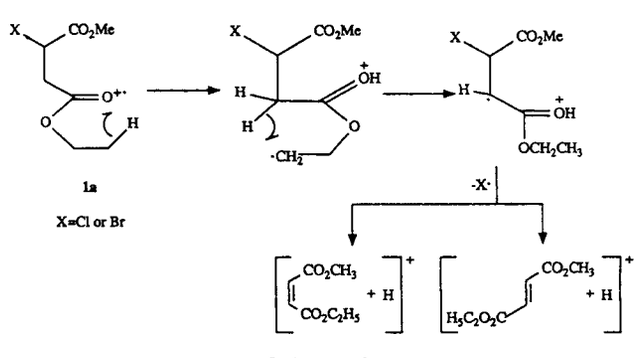


Scheme 1

† Dedicated to Professor H. Budzikiewicz on the occasion of his 60th birthday.

RESULTS AND DISCUSSION

The isomeric methyl ethyl esters **2a** and **2b** of 2-methyl-2-bromosuccinic acid exhibit highly specific behaviour under electron impact (Fig. 1) which is similar to that of **1a** and **1b**: only **2a** eliminates the bromine atom



Scheme 2

0030–493X/93/030230–05 $07.50

Received 20 August 1992
Accepted 28 October 1992

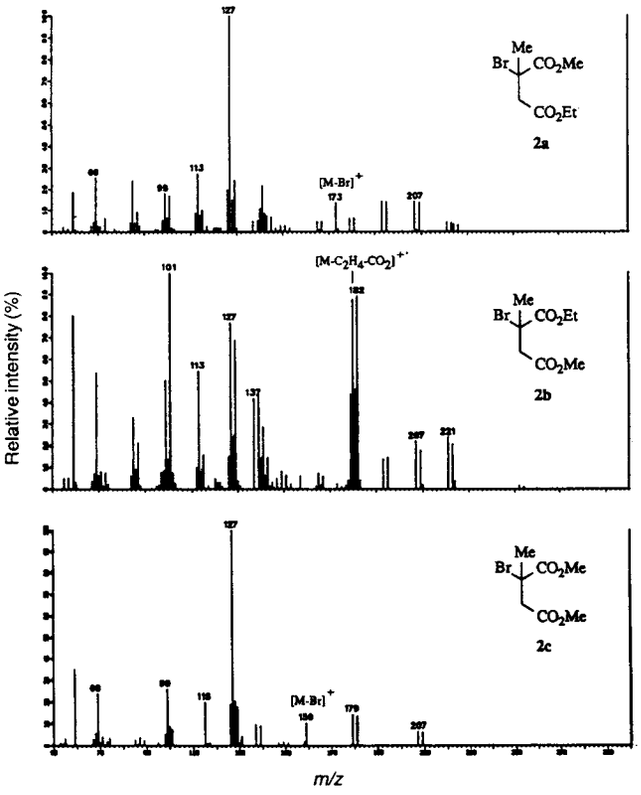
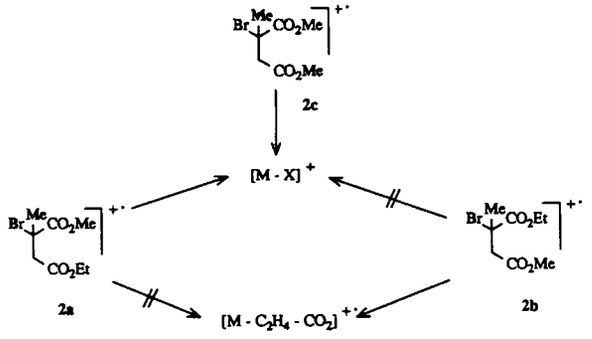


Figure 1. EI mass spectra of **2a**, **2b** and **2c**.

whereas **2b** gives rise to an abundant $[M - C_2H_4 - CO_2]^{+\cdot}$ ion. However, the dimethyl ester **2c** also eliminates Br in sharp contrast to its analogue **1c** (see Scheme 3).



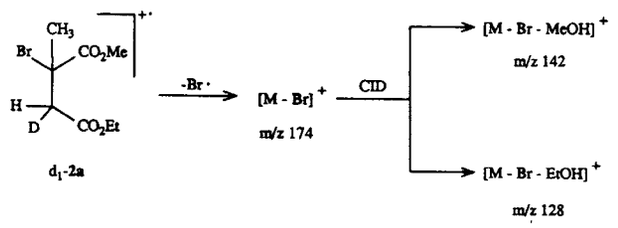
Scheme 3

The different behaviour of **2c** suggests that the mechanism of dehalogenation of 2-methyl-2-halosuccinates **2** is different from that of halosuccinates **1a**. A CID and deuterium-labelling study was undertaken to clarify this point.

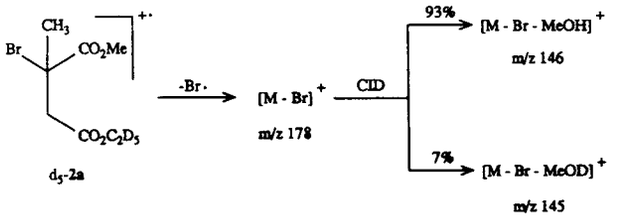
The *m/z* 173 $[M - Br]^+$ ion obtained under electron impact from **2a** gives rise to the following major daughter ions under CID conditions: *m/z* 141 $[M - Br - MeOH]^+$, *m/z* 127 $[M - Br - EtOH]^+$, *m/z* 113 by the loss of CO and/or C_2H_4 from $[M - Br - MeOH]^+$ and *m/z* 99 by elimination of CO from $[M - Br - EtOH]^{+\cdot}$. These ions are almost quantitatively shifted by 1 u to *m/z* 142, 128, 114 and 100 in the CID spectrum of methyl ethyl 3-d_1-2-methyl-2-bromosuccinate, d_1-**2a** (Scheme 4), indicating that virtually no internal hydrogen transfer from position 3 is involved in the elimination of Br from **2a** in contrast to that from **1a**.

Moreover, the *m/z* 178 $[M - Br]^+$ ion obtained from the pentadeuteroethyl analogue d_5-**2a** exhibits major elimination of undeuterated methanol (93%, Scheme 5), which again contrasts the behaviour of **1a** (exclusive loss of CH_3OD, see Scheme 2).

The above results clearly show that the major mechanism of the electron impact-induced dehalogenation of **2a** must differ from that of **1a**. The deuterium-labelling



Scheme 4



Scheme 5

study indicates that the hydrogen atom abstracted in the methanol elimination under CID does not originate at position 3 or at the ethoxyl in **2a**. The only source of hydrogen other than those two positions is the 2-methyl group. These results therefore suggest migration of a

Table 1. Relative ion abundances in the CID spectra of $[M - Br]^+$ ion from 2c and MH^+ ions of dimethyl itaconate (3c), citraconate (4c) and mesaconate (5c).

	Relative abundance (%)[a]			
m/z	$[M - Br]^+$ from 2c[b]	MH^+ of 3c[c]	MH^+ of 4c[c]	MH^+ of 5c[c]
29	0.3	0.0	0.8	1.9
39	0.0	0.1	0.0	2.6
41	0.2	0.3	0.0	1.8
59	0.5	1.5	3.5	11.5
67	0.5	0.1	0.0	0.8
69	6.1	5.9	0.5	32.7
71	0.7	0.8	0.0	4.9
95	0.6	0.9	0.0	2.5
99	22.9	26.1	5.4	100
117	0.4	0.0	0.0	0.0
126	1.8	0.5	0.2	0.0
127	100	100	100	85.8
128	0.0	0.1	0.0	0.5
157	1.4	0.9	0.6	6.7
158	4.3	4.9	8.9	49.1
159	196.2	339.4	264.6	1996

[a] Relative abundances normalized to the most abundant fragment ion.
[b] Ion generated by CE with N_2 at 2.0 mTorr (indicated).
[c] Ion generated by isobutane CI.

Table 2. Relative ion abundances in the CID spectra of $[M - Br]^+$ ion from 2a, d_1-2a and d_5-2a and MH^+ ions of methyl ethyl itaconate (3a), citraconate (4a) and mesaconate (5a)

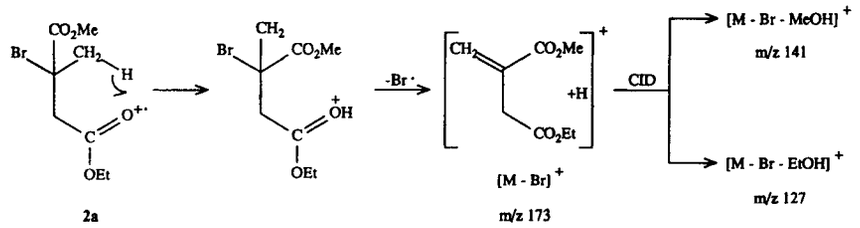
	Relative abundance (%)[a]					
m/z	$[M - Br]^+$ from 2a[b]	MH^+ of 3a[c]	MH^+ of 4a[c]	MH^+ of 5a[c]	$[M - Br]^+$ from d_1-2a[d]	$[M - Br]^+$ from d_5-2a[b]
29	1.5	3.1	2.5	3.2	1.8	
30					0.3	
40						
41	0.3	0.0	0.0	0.0		
42					0.4	
58					0.2	
59	0.8	0.4	2.3	0.0	1.2	0.3
69	2.5	2.5	0.0	2.3		1.4
70					3.4	
71	0.0	1.1	0.0	0.0		
72					0.3	
85	3.2	5.5	0.0	8.7		
86					3.0	0.8
95	0.0	0.9	0.0	0.0		
98						0.8
99	11.6	13.7	2.1	12.3		9.8
100					14.1	
102					0.5	
113	20.3	14.9	30.4	14.8	1.2	0.7
114					19.0	12.2
126	0.7	1.0	1.1	0.0		1.6
127	100	100	100	6.3	2.5	100
128					100	1.0
130					0.7	0.4
131	0.0	0.0	0.0	2.5		
140	0.5	1.2	0.0	0.0		
141	24.7	20.3	30.7	3.7		
142					23.9	
145	2.7	1.9	1.6	100	0.2	2.0
146					0.8	25.9
171	0.5	1.0	1.0	2.6		
172	6.0	8.3	5.5	8.6		
173	254.8	304.9	387.6	530.5	0.3	
174					53.8	
177						7.0
178						442.3

[a] Relative abundances normalized to the most abundant fragment ion.
[b] Ion generated by CE with N_2 at 2.0 mTorr (indicated).
[c] Ion generated by isobutane CI.
[d] Ion generated by EI.

hydrogen atom from the 2-methyl group to a carbonyl oxygen followed by loss of Br, giving rise to protonated itaconate (see Scheme 6).

A similar CID and deuterium-labelling (at C-3) investigation was performed with the dimethyl ester **2c**. The *m/z* 159 $[M - X]^+$ ion obtained under EI from **2c** affords the following daughter ions under CID conditions: *m/z* 127 $[M - X - MeOH]^+$, *m/z* 99 by a subsequent loss of CO and *m/z* 69 by further elimination of CH_2O. In analogy with **2a**, the above three daughter ions are quantitatively shifted by 1 u in the CID spectrum of the *m/z* 160 $[M - X]^+$ ion formed from dimethyl 3-d_1-2-methyl-2-bromosuccinate, d_1-**2c**, to *m/z* 128, 100 and 70, respectively. This result indicates that the mechanism of dehalogenation of **2c** is similar to that of **2a** as shown in Scheme 6.

The comparison of the CID spectrum of the *m/z* 159 $[M - X]^+$ ion from **2c** with those of the protonated molecular ions of dimethyl itaconate, citraconate and mesaconate (see Table 1) provides further support for



Scheme 6

the mechanism suggested in Scheme 6. The CID-induced fragmentation pattern of the $[M - Br]^+$ ion from **2c** is most similar to that of the MH^+ ion obtained from dimethyl itaconate.

The difference in the abundances of the non-reacting parent *m/z* 159 ions can be explained by their lower internal energy content when formed by isobutane chemical ionization (CI) rather than by fragmentation of 2-bromo-2-methylsuccinate **2c** under electron impact (EI). In fact, virtual identity was observed when the CID behaviour of the *m/z* 159 MH^+ ion of dimethyl itaconate (obtained by CI) was compared with that of the $[M - Br]^+$ obtained from **2c** under charge-exchange (CE) conditions with nitrogen at relatively high pressures, where relaxation of more highly excited ions could be expected. However, differences due to different distribution of the proton between the two ester groups in the *m/z* 159 ions (site of protonation isomerism) cannot be readily excluded.

The correlation coefficient[2] in the comparison of CID spectra of protonated dimethyl itaconate and of $[M - Br]^+$ of **2c** is 0.9986 when the parent ion is excluded from calculation (0.9617 for protonated dimethyl citraconate and 0.5434 for dimethyl mesaconate).

CID spectral data for the *m/z* 173 $[M - Br]^+$ ion obtained on CE from the methyl ethyl ester **2a** are given in Table 2, together with those of protonated methyl ethyl itaconate (**3a**), citraconate (**4a**) and mesaconate (**5a**). The correlation coefficient in the comparison of the CID spectrum of the $[M - Br]^+$ ion obtained under nitrogen CE with MH^+ of **3a** is 0.9928. The minor route (7%) leading to elimination of CH_3OD from the $[M - Br]^+$ ion of d_5-**2a** (see Scheme 5) indicates the formation of small amounts of protonated citraconates and mesaconate by the multiple-step mechanism operating with the corresponding chloro- and bromosuccinates **1a** (Scheme 2). It can be expected that an isotope effect operates in this process, and the concentration of protonated citraconate and mesaconate in the $[M - Br]^+$ ions obtained from the unlabelled **2a** is higher than 7%. Comparison of CID data for the $[M - Br]^+$ ion with those calculated for mixtures of protonated itaconates containing moderate proportions of citraconates and mesaconates show better correlations than those obtained for itaconate itself. The correlation coefficient of a 90:9:1 mixture is 0.9952 (0.9928 for protonated itaconate), of a 80:18:2 mixture 0.9970 and of a 66:33:1 mixture 0.9990 (optimum value).

The initial step in the mechanism suggested in Scheme 6 is a 1,5-migration of a hydrogen atom from the 2-methyl group to the 4-carbonyl oxygen via a six-membered ring transition state. There is no possibility of excluding a 1,4-transfer of the 2-methyl hydrogen to the 1-carbonyl oxygen (via a five-membered transition state) on the basis of the experimental data. The distinction between the two possible pathways may be difficult owing to a possible hydrogen bridging between the two ester groups.

1,4-Hydrogen migrations from an α-methyl group play an important role in a number of interesting fragmentation processes induced by EI ionization.[3–7] Among others they have been shown to precede the C—Hal bond cleavage in 2-chloroisobutyrate but not in 2-bromo- and 2-iodoisobutyrates.[6] The present results showing that a hydrogen transfer from the 2-methyl group precedes the C—Br bond cleavage in **2a** and **2c** may indicate that a 1,5- rather than a 1,4-migration precedes the loss of Br.

A further alternative, 1,4-hydrogen migration from the 3-methylene group with subsequent loss of a bromine atom, is obviously of little importance as protonated citraconate (**4c**) and/or mesaconate (**5c**) are, at most, minor products. A reduced proton affinity of the α-halocarboalkoxyl group relative to that of its C(4) counterpart, but also a preference of the six- over five-membered ring transition state, may account for this unexpected selectivity (2-CH_3 vs. 3-CH_2) regarding the abstraction site.

CONCLUSION

The results of the deuterium-labelling and CID studies indicate operation of a single route in the formation of $[M - Br]^+$ ion from the dimethyl ester **2c**, involving migration a hydrogen atom from the 2-methyl group leading to an itaconate structure. This process is the major route leading to $[M - Br]^+$ ions from the ionized 1-methyl-4-ethyl ester **2a** (Scheme 6). A minor route (>7%) involving two migration steps (hydrogen from position 2 of the ethyl group followed by hydrogen from C(3)) leads to the formation of citraconic and mesaconic structures in analogy with the dehalogenation process of 1-methyl-4-ethyl-2-halosuccinates (**1a**) (Scheme 2). The most abundant ion in the mass spectrum of the 1-ethyl-4-methyl ester of 2-methyl-2-bromosuccinic acid (**2b**) is $[M - C_2H_4 - CO_2]^{+\cdot}$. The mechanism of the formation of this ion, which requires an ethoxy group at position 1 (in both **1b** and **2b**), has not yet been clarified, but it presumably involves a hydrogen-transfer step from the ethoxyl to the halogen atom.[1] The absence of an $[M - Br]^+$ ion in the EI mass spectrum of **2b** indicates that the formation of the $[M - C_2H_4 - CO_2]^+$ ion is energetically favoured over the two possible pathways for debromination.

EXPERIMENTAL

Gas chromatography/mass spectrometry (GC/MS) and GC/tandem MS (MS/MS) were performed on a Finnigan MAT TSQ-70 triple-stage quadrupole mass spectrometer coupled to a Varian 3400 gas chromatograph. Mixtures of isomers were separated on a 30 m DB-5 glass capillary column using helium as carrier gas at 12 psi (1 psi = 6895 Pa), the temperature being programmed from 60 to 250 °C at 5 °C min^{-1}. Mass spectra were obtained by EI ionization of the diesters at 70 eV, charge exchange with nitrogen at an indicated pressure of 2.0 mTorr and CI with isobutane. MS/MS was performed in the daughter-ion mode using a 25 eV collision energy and 0.4 mTorr argon target gas pressure (indicated). An MS/MS correction factor

(MSMSC = 70) was applied in order to achieve similar kinetic energies (and similar peak shapes) of the daughter ions irrespective of mass.

Synthesis

The syntheses of **1a**, **1b** and **1c** were described previously.[1]

3a + 3c, 4a + 4c, 5a + 5c. The isomeric methyl ethyl itaconate, citraconate and mesaconate were prepared as mixtures together with the corresponding ethylmethyl and diethyl esters by esterification of the corresponding acids with mixed methanol and ethanol in the presence of sulphuric acid. The mixtures were separated by capillary GC on DB-5, and the structures of the isomers were assigned by comparison with unambiguously synthesized standards.[8] The retention sequence was dimethyl esters < isomers **b** < isomers **a** < diethyl esters.

2b, 2c, d_5-2a. The isomeric methylethyl 2-bromo-2-methylsuccinates and their deuterium isotopomers labelled at the alkoxy groups were prepared as mixtures in the following manner. Concentrated sulphuric acid (0.5 g) was added to a solution of the 2-methylsuccinic acid (10 mmol) and a mixture of the appropriate deuterated and non-deuterated alcohols (20 mmol of each) in dry 1,2-dichloroethane (10 cm^3). After reflux (4 h), the reaction mixture was cooled, saturated sodium chloride solution (10 cm^3) was added and the organic phase was separated, washed with 10% sodium hydrogen carbonate solution, dried and evaporated.

The mixture of esters was refluxed overnight with *N*-bromosuccinimide (NBS) (0.5 g, 2.8 mmol) and a catalytic amount of benzoyl peroxide (0.05 g) in CCl_4, cooled, filtered and the solvent was evaporated. The residue was purified on a short column of silica gel with ethyl acetate–hexane (1:5) as eluent and yielded the mixed esters together with the dimethyl and diethyl esters. The mixtures were subjected to GC/MS under the above conditions and the structures were assigned by comparison with **2a**.

2a. A mixture of 4-ethyl-1-methyl citraconate and mesaconate[8] (570 mg) was hydrogenated on 10% Pd/C in ethanol at room temperature and at 1 atm of hydrogen (1 atm = 101 325 Pa). Evaporation of the solvent yielded 4-ethyl-1-methyl 2-methylsuccinate as a colourless oil (558 mg, 98% yield, pure by TLC, NMR and GC/MS). ^{1}H NMR: δ = 1.19 (d, 3H), 1.23 (t, 3H), 2.35 (dd, 1H), 2.70 (dd, 1H), 2.87 (m, 1H), 3.65 (s, 3H), 4.13 (q, 2H) ppm. NBS bromination (see above) yielded 4-ethyl-1-methyl 2-bromo-2-methylsuccinate (**2a**) (374 mg, 67% yield, pure by TLC, NMR and GC/MS). ^{1}H NMR: δ = 1.22 (t, 3H), 2.01 (s, 3H), 3.03 (d, 1H), 3.43 (d, 1H), 3.78 (s, 3H), 4.11 (q, 2H) ppm.

d_1-2a, d_1-2c. These were prepared by a similar route to **2a** but the Wittig reactions were carried out in a 1:1 mixture of $CDCl_3$ and EtOD. Hydrogenation yielded 4-ethyl-1-methyl 2-methyl-3-*d*-succinate (^{1}H NMR: δ = 1.18 (d, 3H), 1.24 (t, 3H), 2.35 (b, 0.25H), 2.70 (bd, 0.75H), 2.87 (m, 1H), 3.63 (s, 3H), 4.12 (q, 2H) ppm) and dimethyl 2-methyl-3-*d*-succinate (^{1}H NMR: δ = 1.19 (d, 3H), 2.4 (b, 0.3H), 2.7 (bd, 0.7H), 2.91 (m, 1H), 3.65 (s, 3H), 3.67 (s, 3H) ppm).

NBS brominations yielded 4-ethyl-1-methyl 2-methyl-2-bromo-3-*d*-succinate (d_1-**2a**) (^{1}H NMR: δ = 1.22 (t, 3H), 2.01 (s, 3H), 3.03 (b, 0.5H), 3.44 (b, 0.5H), 3.78 (s, 3H), 4.11 (q, 2H) ppm) and dimethyl 2-methyl-2-bromo-3-*d*-succinate (d_1-**2c**) (^{1}H NMR: δ = 2.01 (s, 3H), 3.05 (b, 0.5H), 3.45 (b, 0.5H), 3.67 (s, 3H), 3.79 (s, 3H) ppm). The isotopic composition in both cases was determined by mass spectrometry: d_2 4%, d_1 96%.

Acknowledgements

This work was supported by the Fund for Promotion of Research at the Technion.

REFERENCES

1. D. Bornstein, B. Domon, A. Mandelbaum, D. R. Mueller, W. J. Richter and I. Vidavsky, *Org. Mass Spectrom.* **26**, 793 (1991).
2. T. A. Lehmann, M. M. Bursey and J. R. Hass, *Org. Mass Spectrom.* **18**, 373 (1983).
3. H. Schwarz, *Top. Curr. Chem.* **97**, 1 (1981), and references cited therein.
4. P. C. Burgers, J. L. Holmes, F. P. Lossing, F. R. Povel and J. K. Terlouw, *Org. Mass Spectrom.* **18**, 335 (1983).
5. T. Weiske, H. Halim and H. Schwarz, *Chem. Ber.* **118**, 495 (1985).
6. R. Wolf and H. F. Gruetzmacher, *Org. Mass Spectrom.* **24**, 398 (1989).
7. D. J. McAdoo, C. E. Hudson, T. Lin, L. L. Griffin and J. C. Traeger, *Int. J. Mass Spectrom Ion Processes* **87**, 61 (1989).
8. D. Bornstein, A. Weisz and A. Mandelbaum, *Org. Mass Spectrom.* **21**, 225 (1985).