Collision-induced Dissociations of Carboxylate Negative Ions from 2-Ethylbutanoic, 2-Methylpropanoic, and Pivalic Acids. An Isotopic Labelling Study

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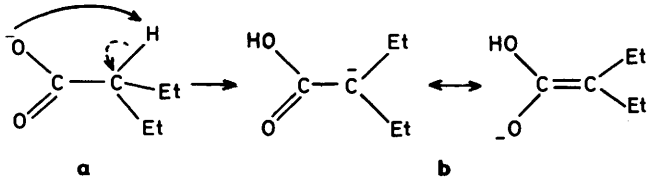
Deprotonation of Et_2CHCO_2H yields $Et_2CHCO_2^-$. On collisional activation this ion forms $CO_2^{-\bullet}$, $CH_2{=}CH^-$, and $MeCH{=}CH^-$. In addition, elimination of H$^\bullet$ and Et$^\bullet$ yield $Et(R)C{=}CO_2^{-\bullet}$ (R = Et and H, respectively). The elimination of Et$^\bullet$ is not a simple cleavage but occurs by loss of H$^\bullet$ from a methyl group followed by loss of ethene. The carboxylate ion also rearranges to $Et_2\bar{C}CO_2H$; this species decomposes to HO^-, $Et\bar{C}{=}CH_2$, and also eliminates the elements of C_3H_8 and CH_4. All fragmentations have been studied using ^2H and ^{13}C labelling: for example it is proposed that loss of CH_4 from $Et_2\bar{C}CO_2H$ occurs by a six-centre stepwise process in which the first step (formation of an incipient methyl anion) is rate determining. The collisional activation mass spectra of $Et_2CHCO_2^-$, $Me_2CHCO_2^-$, and $Me_3CCO_2^-$ are different, all showing characteristic decompositions. For example, all three ions eliminate methane; the mechanism is different in each case.

Collision-induced dissociations of negative ions may be used to provide structural information concerning unknown compounds,[1,2] and also to obtain fundamental information about ion behaviour.[2–4] Carboxylate negative ions have been formed by deprotonation of carboxylic acids using a variety of ionization techniques.[5–30] The characteristic fragmentation of RCO_2^- is decarboxylation to form R^- when R^- is a stabilized species (*e.g.* Ar^-, $CH_2{=}CH{-}CH_2^-$, $HC{\equiv}C{-}CH_2^-$ *etc.*).[2.20–22.31]



a **b**

Little is known of the fragmentations of alkyl carboxylate negative ions RCO_2^-. $Alkyl^-$ ions will not generally be observed since electron affinities are close to zero.† We therefore chose to study the collision-induced fragmentations of the carboxylate ion of 2-ethylbutanoic acid **a** in order to determine what alternative fragmentations occur. In particular we wished to determine whether the conversion **a** into **b** occurs, since we have shown that when carbonyl systems can form two enolate ions (*e.g.* $R^1\bar{C}HCOCH_2R^2$ and $R^1CH_2CO\bar{C}HR^2$), the ions are interconvertible under the conditions of collisional activation.[2.34] If the conversion **a** into **b** does occur, **b** should be readily identifiable by fragmentations through the carbanion centre. A symmetrical alkyl substituent was chosen so that any fragmentations of **b** could be studied using intramolecular isotope effects. During the course of this study it was also necessary to investigate the decompositions of $Me_2CHCO_2^-$ and $Me_3CCO_2^-$.

† The methyl anion (electron affinity 0.08 ± 0.03[32]) can be observed. The acetate anion shows a peak corresponding to Me^- in its collisional activation (c.a.) mass spectrum, *m/z* (‰, structure) 58 (100, $^\bullet CH_2CO_2^-$), 57 (2, $CHCO_2^-$), 44 (1, $CO_2^{-\bullet}$), 41 (4, $HC{\equiv}CO^-$), 40 (1, $C_2O^{-\bullet}$), 17 (0.2, HO^-), 16 (0.1, $O^{-\bullet}$), 15 (2, Me^-), and 14 (0.8, $CH_2^{-\bullet}$). Me^- is also produced in the reaction between MeCDO and 7 eV electrons.[33] In contrast, Et^- is *not* observed in the c.a. mass spectrum of the proprionate anion: *m/z* (‰, composition) 72 (100, $Me\dot{C}HCO_2^-$), 71 (41, $C_3H_3O_2^{-\bullet}$), 70 (9, $C_3H_2O_2^-$), 58 (9, $^\bullet CH_2CO_2^-$), 55 (36, $C_3H_3O^-$), 44 (11, $CO_2^{-\bullet}$), and 27 (7, $C_2H_3^-$).

Results and Discussion

Collisional activation (c.a.) mass spectra were measured using a VG ZAB 2HF mass spectrometer operating in the chemical ionization mode. Deprotonation of carboxylic acids was effected using HO^- or DO^- reagent ions as appropriate. Collision activation was achieved using He in the second collision cell. Full experimental details are recorded in the Experimental section.

Compounds used for this study were (I)—(XV). The c.a. mass spectrum of the title species is shown in the Figure; other spectra are listed in Tables 1, 2, and 4.

Reaction of Et_2CHCO_2D with DO^- gives only an $(M - D)^-$ ion: no $(M - H)^-$ species is observed. In addition, the spectra of the $(M - D)^-$ ion from (I) and the $(M - H)^-$ ion from (II) [produced by reaction of (II) with HO^-] are identical. Thus the carboxylate anion **a** is initially formed exclusively; its c.a. mass spectrum is recorded in the Figure. The spectra of the corresponding ions from the labelled compounds (III)—(IX) are listed in Tables 1 and 2. The Figure shows a number of complex collision-induced fragmentations, and the data in Tables 1 and 2 show that a number of fragmentations can only be explained by the intermediacy of the enolate **b**. All fragmentations are specific: neither carbon nor hydrogen randomization precedes or accompanies any decomposition.

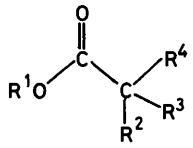
Fragmentation of the Enolate Ion.—Consider first those peaks in the Figure which arise by fragmentation of enolate **b**. The data in Tables 1 and 2 allow the following proposals to be made (see Scheme 1). (i) The specific production of DO^- from '$Et_2CDCO_2^-$' suggests that HO^- is formed as shown in equation (1). (ii) The formation of $C_4H_7^-$ (*m/z* 55) involves loss of the elements of acetic acid, including the hydrogen of the original CH group: a plausible mechanism is shown in equation (2). (iii) The formation of *m/z* 71 can occur by one of two mechanisms; either the Me^- elimination reaction shown in equation (3), or, and less likely, an Me^- S_Ni reaction resulting in elimination of C_3H_8. In either case, the product ion is one of the stabilized forms (**c**) of deprotonated acrylic acid (*cf.* ref. 35); this is supported experimentally

Table 1. C.a. mass spectra of carboxylate negative ions from (III)—(X). The losses of H$^{\cdot}$, CH_4, $C_2H_5^{\cdot}$, and C_3H_8 and labelled analogues

	Loss									
Anion	H$^{\cdot}$	D$^{\cdot}$	CH_4	CH_3D	CD_3H	$^{13}CH_4$	$C_2H_5^{\cdot}$	$C_2H_3D_2^{\cdot}$	$C_2H_2D_3^{\cdot}$	$^{12}C^{13}CH_5^{\cdot}$
$^-O_2CCDEt_2$	45	55		16			100			
$^-O_2CCH(CD_2Me)_2$	100		20					84		
$^-O_2CCH(CD_2Me)Et$	100		21				46.2[a]	44.0[a]		
$^-O_2CCH(CH_2CD_3)_2$	44	76			16				100	
$^-O_2CCH(CH_2CD_3)Et$	100	55	12		12		85.1[a]		43.0[a]	
$^-O_2CCH(^{13}CH_2Me)(CH_2{}^{13}CH_3)$	100		9.8			8.5				93
$^-O_2CCH(^{13}CH_2Me)Et$	100		18				45.0[a]			44.6[a]
$^-O_2CCH(CH_2{}^{13}CH_3)Et$	100		10.1[a]			8.9[a]	46.1[a]			46.1[a]

	Loss					
Anion	C_3H_8	$C_3H_6D_2$	$C_3H_5D_3$	$C_3H_2D_6$	$^{12}C_2{}^{13}CH_8$	$^{12}C^{13}C_2H_8$
$^-O_2CCDEt_2$	28					
$^-O_2CCH(CD_2Me)_2$		26				
$^-O_2CCH(CD_2Me)Et$	12.3[a]	10.1[a]				
$^-O_2CCH(CH_2CD_3)_2$				21		
$^-O_2CCH(CH_2CD_3)Et$			36			
$^-O_2CCH(^{13}CH_2Me)(CH_2{}^{13}CH_3)$					11.0[b]	11.0[b]
$^-O_2CCH(^{13}CH_2Me)Et$	10.5[b]				10.5[b]	
$^-O_2CCH(CH_2{}^{13}CH_3)Et$					25	

[a] An average of ten scans. [b] Unresolved; the composite peak for *m/z* 71 and 72 is exactly gaussian with a peak maximum at 71.50 a.m.u.



	R^1	R^2	R^3	R^4
(I)	D	H	Et	Et
(II)	H	H	Et	Et
(III)	D	D	Et	Et
(IV)	H	H	CD_2Me	CD_2Me
(V)	H	H	CD_2Me	Et
(VI)	H	H	CH_2CD_3	CH_2CD_3
(VII)	H	H	CH_2CD_3	Et
(VIII)	H	H	$^{13}CH_2Me$	$CH_2{}^{13}CH_3$
(IX)	H	H	$^{13}CH_2Me$	Et
(X)	H	H	Et	$CH_2{}^{13}CH_3$
(XI)	H	H	Me	Me
(XII)	D	D	Me	Me
(XIII)	H	H	CD_3	CD_3
(XIV)	H	H	CD_3	Me
(XV)	H	Me	Me	Me

Table 2. C.a. mass spectra of carboxylate negative ions from (III)—(X). The formation of HCO_2^-, $CO_2^{-\cdot}$, $C_3H_5^-$, $C_2H_3^-$, HO^- and labelled analogues

	Formation						
Anion	$C_4H_7^-$	$C_4H_5D_2^-$	$C_4H_4D_3^-$	$C_4H_3D_4^-$	$^{12}C_3{}^{13}CH_7^-$	$^{12}C_2{}^{13}C_2H_7^-$	$CO_2^{-\cdot}$
$^-O_2CCDEt_2$	2						5
$^-O_2CCH(CD_2Me)_2$				2			4
$^-O_2CCH(CD_2Me)Et$		2					4
$^-O_2CCH(CH_2CD_3)_2$			2				5
$^-O_2CCH(CH_2CD_3)Et$	1.0[a]		1.0[a]				5
$^-O_2CCH(^{13}CH_2Me)(CH_2{}^{13}CH_3)$					0.8[a]	0.8[a]	4
$^-O_2CCH(^{13}CH_2Me)Et$					2		4
$^-O_2CCH(CH_2{}^{13}CH_3)Et$	0.9[a]				0.9[a]		5

	Formation										
Anion	$C_3H_5^-$	$C_3H_4D^-$	$C_3H_3D_2^-$	$C_3H_2D_3^-$	$^{12}C_2{}^{13}CH_5^-$	$C_2H_3^-$	$C_2H_2D^-$	$C_2HD_2^-$	$^{12}C^{13}CH_3^-$	HO^-	DO^-
$^-O_2CCDEt_2$		2					1				1
$^-O_2CCH(CD_2Me)_2$								1		1	
$^-O_2CCH(CD_2Me)Et$	1	0.7				0.5[a]		0.5[a]		1	
$^-O_2CCH(CH_2CD_3)_2$				b		1				1	
$^-O_2CCH(CH_2CD_3)Et$	1			b		1				1	
$^-O_2CCH(^{13}CH_2Me)(CH_2{}^{13}CH_3)$						0.5[a]			0.5[a]	1	
$^-O_2CCH(^{13}CH_2Me)Et$	1.0[a]				1.0[a]	0.6[a]			0.6[a]	1	
$^-O_2CCH(CH_2{}^{13}CH_3)Et$	1.5					1				1	

[a] An average of 10 scans. [b] Both $CO_2^{-\cdot}$ and $C_3H_2D_3^-$ correspond to *m/z* 44.

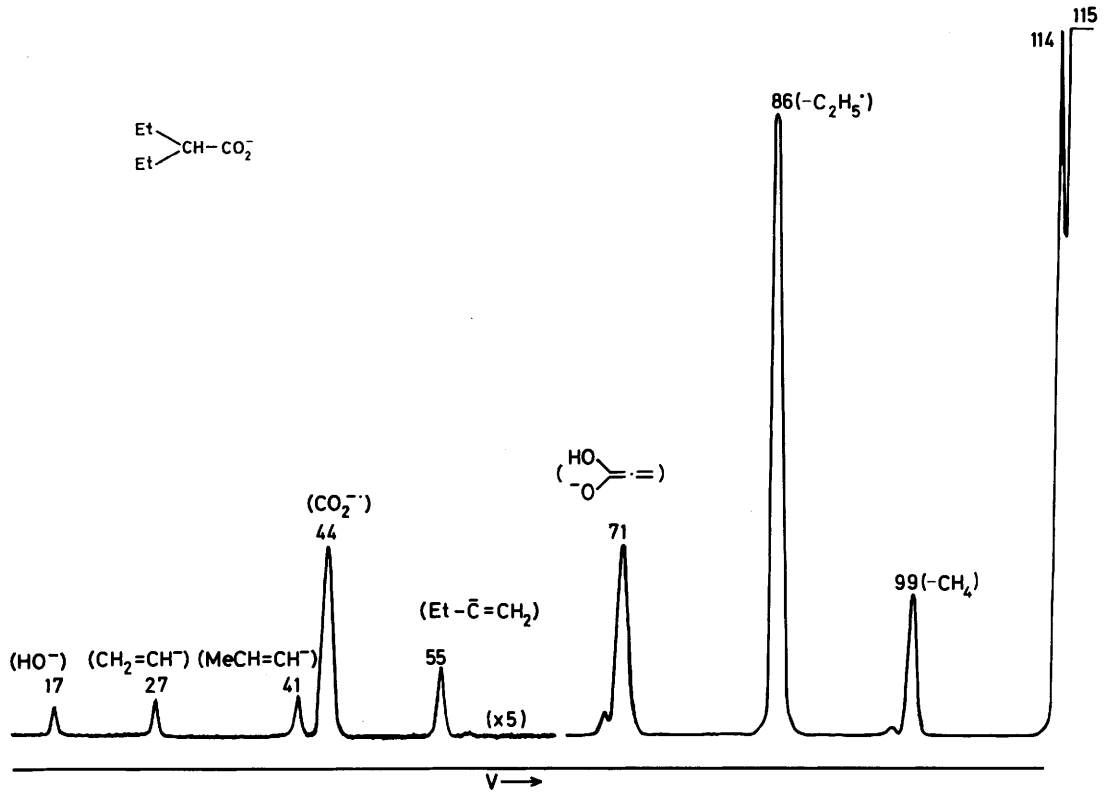
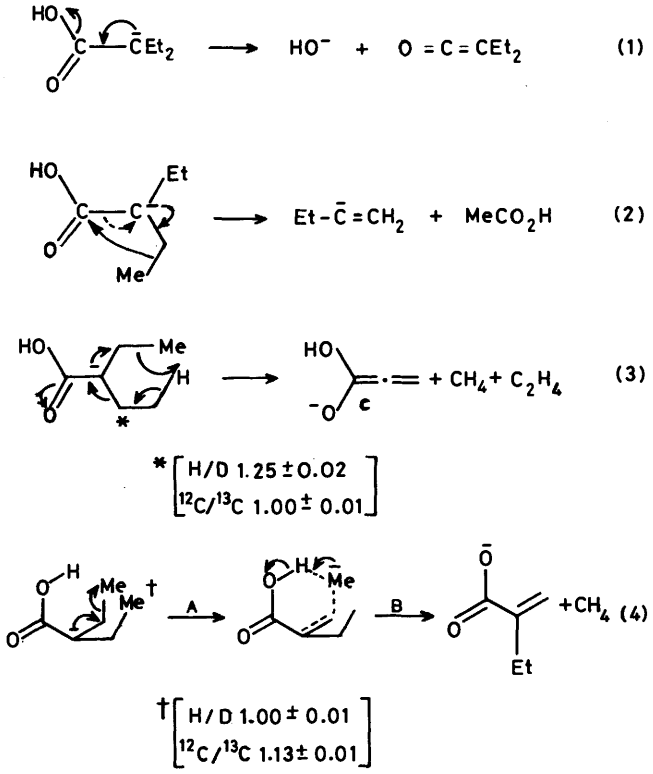


Figure. C.a. mass spectrum of the $(M - D)^-$ ion from $DO_2CCH(Et)_2$. Experimental conditions, see Experimental section. The width of major peaks at half height are: *m/z* (V) 99 (68.2), 86 (63.4), 71 (87.5), 55 (51.7), 44 (53.6), and 41 (51.0). When a voltage of 1 kV is applied to the second collision cell all peaks were shown to be collision induced except for *m/z* 86 which had a small unimolecular component (collision induced: unimolecular 95:5)

Table 3. C.a. and c.r. mass spectra of the acrylic acid $(M - H)^-$ ion

C.a. m.s.: *m/z* (%, loss); 70 (100, H•), 69 (15, H_2), 44 (48, C_2H_3•), 27 (28, CO_2)

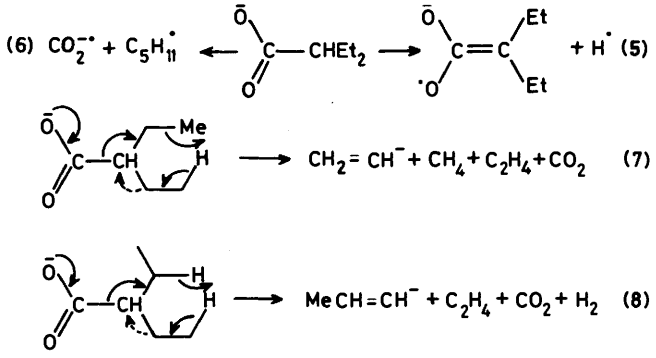
C.r. (positive ion) m.s.: *m/z* (%); 56 (8), 55 (11), 53 (9), 45 (13), 44 (72), 41 (13), 39 (8), 37 (9), 29 (18), 28 (36), 27 (100), 26 (92), 25 (38), 24 (12), 16 (5), 15 (4), 14 (7), 13 (7), 12 (5)



Scheme 1.

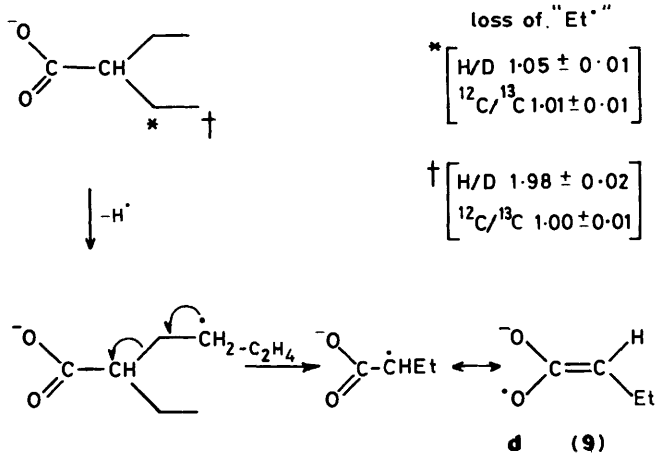
since the c.a. mass spectrum and charge-reversal (positive ion) mass spectrum[36] of *m/z* 71 and deprotonated acrylic acid are identical (see Table 3). The kinetic isotope effect [shown in equation (3)] favours a stepwise reaction in which the first step (incipient Me^- formation) is rate determining. (iv) The loss of methane (to form *m/z* 99) occurs as shown in equation (4). The kinetic isotope effects [listed under equation (4)] suggest that step A is rate determining.

Fragmentations of the Carboxylate Anion.—A number of ions are formed by direct fragmentation of the carboxylate ion **a** (see Schemes 2 and 3). In summary: (i) there are *two* specific losses of H•. The minor loss occurs as shown in equation (5). The major loss is unexpected since it involves loss of a hydrogen atom from a terminal methyl group. It is not clear whether this is a reaction of enolate **b** or carboxylate **a**. Perhaps the driving force for the reaction is the ultimate formation of a stabilized cyclised ion; (ii) $CO_2^{-\bullet}$ formation occurs from **a** [see equation (6)]; (iii) the ions $C_2H_3^-$ (*m/z* 27) and $C_3H_5^-$ (*m/z* 41) are formed in small abundance. Both retain the CH moiety and are thus formed from **a** [see *e.g.* equations (7) and (8)*]; (iv) the major peak at



Scheme 2.

m/z 86 is formed by loss of the elements of C_2H_5•, and it might be predicted that this reaction should be a simple cleavage analogous to that shown in equation (5). Yet this cannot be correct because of the isotope effect data shown for this loss in Scheme 3.



Scheme 3.

The isotope effect data shown in Scheme 3 must mean that the loss of Et• involves either initial loss or migration of a methyl hydrogen in the rate-determining step of the reaction. In order to investigate this reaction further we studied the loss of Me• from the analogous 2-methylpropionate anion. The c.a. mass spectra of this and labelled analogues are listed in Table 4. The ratio of losses of Me• and CD_3• in the c.a. mass spectrum of $Me(CD_3)CHCO_2^-$ is 1.1:1. Thus, the losses of Me• and Et• respectively from $Me_2CHCO_2^-$ and $Et_2CHCO_2^-$ must occur by different mechanisms.

It seems likely that the structure of *m/z* 86 is **d** (Scheme 3) since its c.a. mass spectrum shows losses of H• and Me•, while its charge-reversal spectrum contains a peak due to $CO_2^{+\bullet}$ (see Table 5). Two possible mechanisms for the loss of Et• must be considered: (i) proton transfer from a methyl group to O^- precedes elimination of H• and ethene, or (ii) the reaction is stepwise with initial H• loss being rate determining followed by elimination of ethene. The first proposal has an analogy in the loss of Me• from the acetaldehyde molecular *cation*.[37] However, if such a mechanism does operate, the c.a. mass spectrum of $(CD_3CH_2)CHCO_2^-$ would show a DO^- ion. *No such ion is observed.* We thus propose the mechanism shown in Scheme 3; this is supported by the observation that the major loss of H• from $Et_2CHCO_2^-$ originates from a methyl substituent (see above).

* The alternative reaction where H^- effects an S_Ni reaction to eliminate CO_2 and C_2H_6 seems a less likely possibility.

Table 4. C.a. mass spectra of carboxylate anions from (XI)—(XIV)

	Loss									
Anion	$H^{\bullet}$	$D^{\bullet}$	H_2	HD	$CH_3^{\bullet}$	$CD_3^{\bullet}$	CH_4	CH_3D	CD_3H	CD_4
$^-O_2CCHMe_2$	100		40		23		15			
$^-O_2CCDMe_2$		100		32	20		14			
$^-O_2CCH(CD_3)_2$	100			35		19				10
$^-O_2CCH(CD_3)Me$	100		22	12	10	9.5		7.5	8.0	
$^-O_2CCMe_3$					92		78			

	Formation									
Anion	$CO_2^{-\bullet}$	$C_3H_5^-$	$C_3H_4D^-$	$C_3H_3D_2^-$	$C_3H_2D_3^-$	$C_3D_5^-$	$C_2H_3^-$	$C_2H_2D^-$	$C_2HD_2^-$	HO^-	DO^-
$^-O_2CCHMe_2$	65	14					4			2	
$^-O_2CCDMe_2$	62	12						3			2
$^-O_2CCH(CD_3)_2$	58					6			3	2	
$^-O_2CCH(CD_3)Me$	68			8	*a*		2		1.5	2	
$^-O_2CCMe_3$	100										

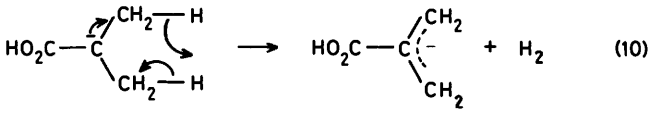
[a] $CO_2^{-\bullet}$ and $C_3H_2D_3^-$ both 44 a.m.u.

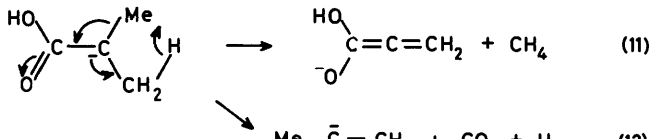
Table 5. C.a. and c.r. mass spectra of *m/z* 86 from $Et_2CHCO_2^-$

C.a. m.s., *m/z* (%, loss): 85 (78, $-H^{\bullet}$), 71 (100, $-Me^{\bullet}$), 27 (2, $-C_2H_3O_2^{\bullet}$)

C.r. (positive ion) m.s., *m/z* (%): 58 (12), 57 (14), 56 (16), 44 (42, $CO_2^{+\bullet}$), 41 (72), 39 (100, $C_3H_3^+$), 29 (82), 28 (66), 27 (92, $C_2H_3^+$), 15 (12, CH_3^+), 14 (8, $CH_2^{+\bullet}$), 13 (6, CH^+)

The 2-Methylpropanoate and Pivalate Negative Ions.—The c.a. mass spectra of (XI)—(XV) are recorded in Table 4. Some of the fragmentations of $Me_2CHCO_2^-$ are similar to those of $Et_2CHCO_2^-$, *e.g.* losses of $H^{\bullet}$ [*cf.* equation (5)], $Me^{\bullet}$ [*cf.* equation (5)], and the formation of $CO_2^{-\bullet}$ [*cf.* equation (6)]. Some fragmentations are however quite different, *viz.* eliminations of H_2 [equation (10)], CH_4 [equation (11)], and the formation of $C_3H_5^-$ [the atoms involved are shown in equation (12)].


(10)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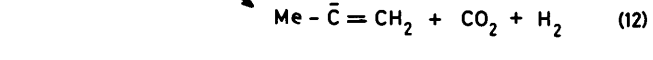
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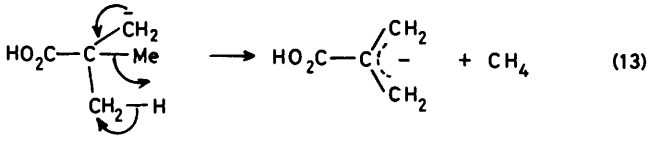
(13)

In contrast, the pivalate anion $Me_3CCO_2^-$ (Table 4) cannot eliminate H_2 since it cannot form an enolate ion, but loss of $Me^{\bullet}$ [*cf.* equation (5)] and the formation of $CO_2^{-\bullet}$ [*cf.* equation (6)] are observed. Interestingly, methane is eliminated: this must occur by the mechanism shown in equation (13).

In conclusion, we have shown that alkyl carboxylate ions $R_2CHCO_2^-$ (R = Me and Et) on collisional activation undergo proton transfer to yield the enolate ion R_2CCO_2H, and that both carboxylate and enolate ions undergo complex but characteristic fragmentations. When there is no hydrogen at position 1 (as in $Me_3CCO_2^-$) the enolate ion cannot be formed: in this case fragmentation occurs through both the carboxylate ion and $^-CH_2(Me)_2CCO_2H$.

Experimental

C.a. mass spectra and charge-reversal mass spectra[36] were recorded on a VG ZAB 2HF mass spectrometer. All slits were fully open to obtain maximum sensitivity and to minimize energy-resolution effects.[38] The chemical ionization slit was used in the ion source: ionizing energy 100 eV (tungsten filament), ion source temperature 180 °C, accelerating voltage 8 kV. Carboxylate anions were generated by ^1H abstraction from compounds (II), (IV)—(XI), and (XIII)—(XV) by HO^- (or H^- or $O^{-\bullet}$) or from (I), (III), and (XII) by ^2H abstraction by DO^- (or D^- or $O^{-\bullet}$). Reactant negative ions were generated from either H_2O or D_2O by 100 eV electrons.[39] The indicated source gauge pressure (of H_2O or D_2O) was typically 1×10^{-5} mbar. The carboxylic acid pressure was typically 5×10^{-6} mbar. The estimated total pressure within the source is 10^{-1} mbar. The pressure of He in the second collision cell was 2×10^{-7} mbar, measured by an ion gauge situated between the electric sector and the second collision cell. This produced a decrease in the main beam signal of *ca.* 10% and thus corresponds to essentially single collision conditions.

Compounds (II), (XI), and (XIV) were commercially available. Compound (I) was produced by treating (II) (1 g) with deuterium oxide (3 × 2 ml) at 25 °C for 3 h ($^2H_1$ 98%).

Compounds (III) and (XII) were made by reduction of the α-bromo derivatives of (II) and (XI) using Zn–D_2O.[40]

Compounds (V), (VII), (IX), and (X) were made from the reactions of butanoic acid with the commercially available $MeCD_2I$ ($^2H_2$ > 99%), CD_3CH_2I ($^2H_3$ > 99%), $Me^{13}CH_2I$ (^{13}C 91%), and $^{13}CH_3CH_2I$ (^{13}C 91%), using a modification of the method of Creger.[41] Yields were 75—85%. The following example describes the method used.

2-[1,1-$^2H_2$]*Ethylbutanoic Acid* (V).—To a suspension of sodium hydride (62 mg, 60% in oil) in di-isopropylamine (162 mg) and tetrahydrofuran (3 ml) under nitrogen, was added butanoic acid (132 mg). After heating to reflux, the mixture was cooled to 0 °C, and n-butyl-lithium in hexane (1.0 ml, 1.6M) was added. The mixture was warmed to 30 °C, then cooled to 0 °C, [1,1-$^2H_2$]ethyl iodide (235.5 mg) was added, the mixture stirred at 20 °C for 4.5 h, poured into water (20 ml), and the organic layer separated. The aqueous layer was acidified with aqueous

hydrogen chloride (2N) and extracted with diethyl ether (6 × 6 ml). The combined organic extract was washed with aqueous sodium hydrogensulphite (20%; 6 ml), water (6 ml), aqueous sodium chloride (saturated; 6 ml), dried ($MgSO_4$), and the solvent removed. The residual oil was distilled (85—100 °C at 13 mmHg) in a T tube to give 2-[1,1-$^2H_2$]ethylbutanoic acid (**V**) as a liquid [133 mg, 76% yield, containing a trace of butanoic acid (< 5%)]. Preparative g.c. on 20% SE-30 on Chromosorb A (AW) (60—80 mesh) in a glass 6 mm × 3 m column at 185 °C using N_2 carrier gas (flow rate 40 ml min) gave the pure acid.

Compounds (**IV**), (**VI**), and (**VIII**) were made by similar procedures; that for the preparation of (**IV**) is typical.

2-[1,1-$^2H_2$]*Ethyl*-[3,3-$^2H_2$]*butanoic Acid* (**IV**).—(i) *Diethyl* [1,1-$^2H_2$]*ethylmalonate.* Potassium (59 mg) was added to t-butyl alcohol (3 ml) under nitrogen at 20 °C, and stirring was continued until all the potassium had dissolved. Diethyl malonate (240 mg) was then added, the mixture was stirred at 20 °C for 15 min, [1,1-$^2H_2$]ethyl iodide (355 mg) was added, and the mixture heated at reflux for 5 h. t-Butyl alcohol was removed by fractional distillation, water (25 ml) was added, and the mixture extracted with diethyl ether (3 × 12 ml). The combined organic extract was washed with water (2 × 12 ml) and aqueous sodium chloride (saturated; 12 ml), dried ($MgSO_4$), and the solvent removed to give the product as an oil (242 mg, crude yield 87%).

(ii) *Diethyl di-*[1,1-$^2H_2$]*ethylmalonate.* Crude diethyl [1,1-$^2H_2$]ethylmalonate (242 mg) was converted into diethyl di-[1,1-$^2H_2$]ethylmalonate (258 mg, crude yield 91%) by the method described in (i) above.

(iii) 2-[1,1-$^2H_2$]*Ethyl*-[3,3-$^2H_2$]*butanoic acid* (**IV**). A modification of the method of Krapcho was used.[42]

Crude diethyl di-[1,1-$^2H_2$]ethylmalonate (258 mg), dimethyl sulphoxide (4.5 ml), water (42 μl), and lithium chloride (108 mg) were heated under reflux (under nitrogen) for 6 h, the mixture was allowed to cool to 20 °C, poured into water (20 ml), sodium chloride (1.0 g) was added, and the mixture extracted with light petroleum (b.p. 40—50 °C; 2 × 10 ml). The combined organic extract was washed with water (2 × 10 ml), aqueous sodium chloride (saturated; 10 ml), dried ($MgSO_4$), and the solvent removed to give crude ethyl 2-[1,1-$^2H_2$]ethyl-[3,3-$^2H_2$]butanoate as a yellow oil (201 mg). To this oil was added aqueous sodium hydroxide (5%; 5 ml), and the mixture was heated under reflux for 4.5 h, cooled to 20 °C, poured into water (20 ml), and extracted with diethyl ether (2 × 10 ml). The aqueous layer was acidified with aqueous hydrogen chloride (2N) and extracted with diethyl ether (4 × 10 ml). The combined organic extracts were washed with water (10 ml), aqueous sodium chloride (saturated; 10 ml), dried ($MgSO_4$), and the solvent removed to give a pale yellow oil which was distilled (T-tube; 90—100 °C at 12 mmHg) to yield crude (**IV**) (85 mg, 61%) which was purified by preparative g.c. as outlined for (**V**) above.

2-[$^2H_3$]Methylpropanoic acid (**XIV**) was prepared from propanoic acid and [$^2H_3$]methyl iodide by the method outlined above for (**V**). 2-[$^2H_3$]Methyl-[3,3,3-$^2H_3$]propanoic acid (**XIII**) was prepared from diethyl malonate by an identical procedure to that used for (**IV**) above.

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