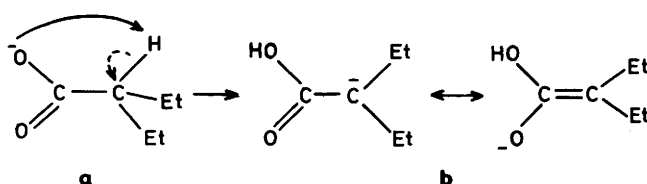


Collision-induced Dissociations of Carboxylate Negative Ions from 2-Ethylbutanoic, 2-Methylpropanoic, and Pivalic Acids. An Isotopic Labelling Study

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Deprotonation of $\text{Et}_2\text{CHCO}_2\text{H}$ yields $\text{Et}_2\text{CHCO}_2^-$. On collisional activation this ion forms CO_2^- , $\text{CH}_2=\text{CH}^-$, and $\text{MeCH}=\text{CH}^-$. In addition, elimination of H^\bullet and Et^\bullet yield $\text{Et(R)C}=\text{CO}_2^-$ ($\text{R} = \text{Et}$ 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 $\text{Et}_2\text{CCO}_2\text{H}$; this species decomposes to HO^- , $\text{Et}\text{C}=\text{CH}_2$, 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 $\text{Et}_2\text{CCO}_2\text{H}$ 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 $\text{Et}_2\text{CHCO}_2^-$, $\text{Me}_2\text{CHCO}_2^-$, and $\text{Me}_3\text{CCO}_2^-$ 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^- , $\text{CH}_2=\text{CH}-\text{CH}_2^-$, $\text{HC}\equiv\text{C}-\text{CH}_2^-$ etc.).^{2,20-22,31}



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. $\text{R}^1\text{CHCOCH}_2\text{R}^2$ and $\text{R}^1\text{CH}_2\text{COCHR}^2$), 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 $\text{Me}_2\text{CHCO}_2^-$ and $\text{Me}_3\text{CCO}_2^-$.

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 $\text{Et}_2\text{CHCO}_2\text{D}$ with DO^- gives only an $(M - \text{D})^-$ ion: no $(M - \text{H})^-$ species is observed. In addition, the spectra of the $(M - \text{D})^-$ ion from (I) and the $(M - \text{H})^-$ 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.

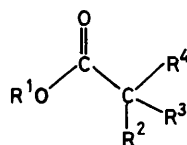
Fragmentation of the Enolate Ion.—Consider first those peaks in the Figure which arise by fragmentation of enolate **b**. The data in Tables 1 and 2 allow the following proposals to be made (see Scheme 1). (i) The specific production of DO^- from $^t\text{Et}_2\text{CDCO}_2^-$ suggests that HO^- is formed 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^- $\text{S}_{\text{N}}\text{i}$ 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

[†] 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, $^t\text{CH}_2\text{CO}_2^-$), 57 (2, CHCO_2^-), 44 (1, CO_2^-), 41 (4, $\text{HC}\equiv\text{CO}^-$), 40 (1, C_2O^-), 17 (0.2, HO^-), 16 (0.1, O^-), 15 (2, Me^-), and 14 (0.8, CH_2^-). 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 propionate anion: m/z (% composition) 72 (100, MeCHCO_2^-), 71 (41, $\text{C}_3\text{H}_3\text{O}_2^-$), 70 (9, $\text{C}_3\text{H}_2\text{O}_2^-$), 58 (9, $^t\text{CH}_2\text{CO}_2^-$), 55 (36, $\text{C}_3\text{H}_3\text{O}^-$), 44 (11, CO_2^-), and 27 (7, C_2H_3^-).

Table 1. C.a. mass spectra of carboxylate negative ions from (III)–(X). The losses of H[•], CH₄, C₂H₅[•], and C₃H₈ and labelled analogues

Anion	Loss									
	H [•]	D [•]	CH ₄	CH ₃ D	CD ₃ H	¹³ CH ₄	C ₂ H ₅ [•]	C ₂ H ₃ D ₂ [•]	C ₂ H ₂ D ₃ [•]	¹² C ¹³ CH ₅ [•]
⁻ O ₂ CCDEt ₂	45	55		16			100			
⁻ O ₂ CCH(CD ₂ Me) ₂	100		20					84		
⁻ O ₂ CCH(CD ₂ Me)Et	100		21				46.2 ^a	44.0 ^a		
⁻ O ₂ CCH(CH ₂ CD ₃) ₂	44	76			16				100	
⁻ O ₂ CCH(CH ₂ CD ₃)Et	100	55	12		12		85.1 ^a		43.0 ^a	
⁻ O ₂ CCH(¹³ CH ₂ Me)(CH ₂ ¹³ CH ₃)	100		9.8			8.5				93
⁻ O ₂ CCH(¹³ CH ₂ Me)Et	100		18				45.0 ^a			44.6 ^a
⁻ O ₂ CCH(CH ₂ ¹³ CH ₃)Et	100		10.1 ^a			8.9 ^a	46.1 ^a			46.1 ^a

Anion	Loss					
	C ₃ H ₈	C ₃ H ₆ D ₂	C ₃ H ₅ D ₃	C ₃ H ₂ D ₆	¹² C ₂ ¹³ CH ₈	¹² C ¹³ C ₂ H ₈
⁻ O ₂ CCDEt ₂	28					
⁻ O ₂ CCH(CD ₂ Me) ₂		26				
⁻ O ₂ CCH(CD ₂ Me)Et	12.3 ^a	10.1 ^a				
⁻ O ₂ CCH(CH ₂ CD ₃) ₂				21		
⁻ O ₂ CCH(CH ₂ CD ₃)Et			36			
⁻ O ₂ CCH(¹³ CH ₂ Me)(CH ₂ ¹³ CH ₃)					11.0 ^b	11.0 ^b
⁻ O ₂ CCH(¹³ CH ₂ Me)Et	10.5 ^b				10.5 ^b	
⁻ O ₂ CCH(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 ₂ Me	CD ₂ Me
(V)	H	H	CD ₂ Me	Et
(VI)	H	H	CH ₂ CD ₃	CH ₂ CD ₃
(VII)	H	H	CH ₂ CD ₃	Et
(VIII)	H	H	¹³ CH ₂ Me	CH ₂ ¹³ CH ₃
(IX)	H	H	¹³ CH ₂ Me	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^- , C_3H_5^- , C_2H_3^- , HO^- and labelled analogues

Anion	Formation						
	C_4H_7^-	$\text{C}_4\text{H}_5\text{D}_2^-$	$\text{C}_4\text{H}_4\text{D}_3^-$	$\text{C}_4\text{H}_3\text{D}_4^-$	$^{12}\text{C}_3^{13}\text{CH}_7^-$	$^{12}\text{C}_2^{13}\text{C}_2\text{H}_7^-$	CO_2^-
$^-\text{O}_2\text{CCDEt}_2$	2						5
$^-\text{O}_2\text{CCH}(\text{CD}_2\text{Me})_2$				2			4
$^-\text{O}_2\text{CCH}(\text{CD}_2\text{Me})\text{Et}$		2					4
$^-\text{O}_2\text{CCH}(\text{CH}_2\text{CD}_3)_2$			2				5
$^-\text{O}_2\text{CCH}(\text{CH}_2\text{CD}_3)\text{Et}$	1.0 ^a		1.0 ^a				5
$^-\text{O}_2\text{CCH}(^{13}\text{CH}_2\text{Me})(\text{CH}_2^{13}\text{CH}_3)$					0.8 ^a	0.8 ^a	4
$^-\text{O}_2\text{CCH}(^{13}\text{CH}_2\text{Me})\text{Et}$					2		4
$^-\text{O}_2\text{CCH}(\text{CH}_2^{13}\text{CH}_3)\text{Et}$	0.9 ^a				0.9 ^a		5

Anion	Formation									
	C_3H_5^-	$\text{C}_3\text{H}_4\text{D}^-$	$\text{C}_3\text{H}_3\text{D}_2^-$	$\text{C}_3\text{H}_2\text{D}_3^-$	$^{12}\text{C}_2^{13}\text{CH}_5^-$	C_2H_3^-	$\text{C}_2\text{H}_2\text{D}^-$	C_2HD_2^-	$^{12}\text{C}^{13}\text{CH}_3^-$	HO^- DO^-
$^-\text{O}_2\text{CCDEt}_2$		2					1			1
$^-\text{O}_2\text{CCH}(\text{CD}_2\text{Me})_2$								1		1
$^-\text{O}_2\text{CCH}(\text{CD}_2\text{Me})\text{Et}$	1	0.7				0.5 ^a		0.5 ^a		1
$^-\text{O}_2\text{CCH}(\text{CH}_2\text{CD}_3)_2$				<i>b</i>		1				1
$^-\text{O}_2\text{CCH}(\text{CH}_2\text{CD}_3)\text{Et}$	1			<i>b</i>		1				1
$^-\text{O}_2\text{CCH}(^{13}\text{CH}_2\text{Me})(\text{CH}_2^{13}\text{CH}_3)$						0.5 ^a			0.5 ^a	1
$^-\text{O}_2\text{CCH}(^{13}\text{CH}_2\text{Me})\text{Et}$	1.0 ^a				1.0 ^a	0.6 ^a			0.6 ^a	1
$^-\text{O}_2\text{CCH}(\text{CH}_2^{13}\text{CH}_3)\text{Et}$	1.5					1				1

^a An average of 10 scans. ^b Both CO_2^- and $\text{C}_3\text{H}_2\text{D}_3^-$ correspond to m/z 44.

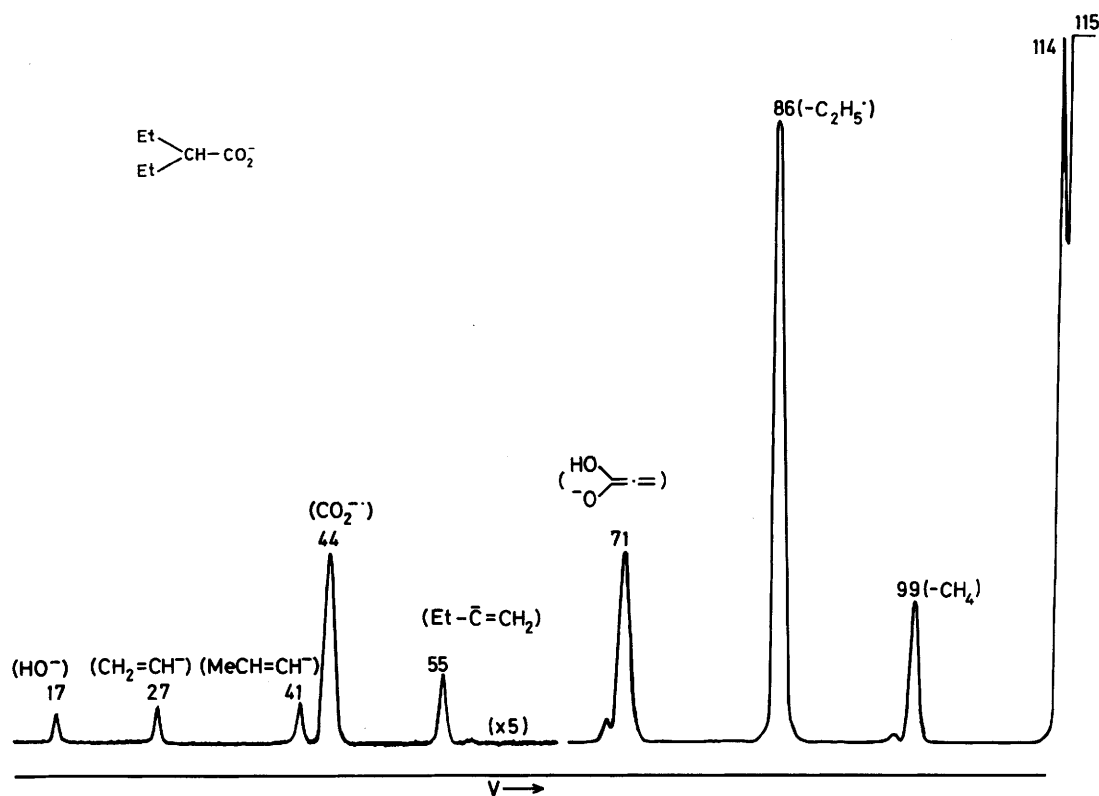
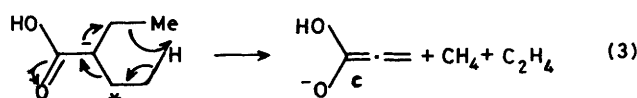
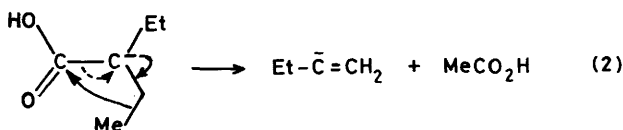
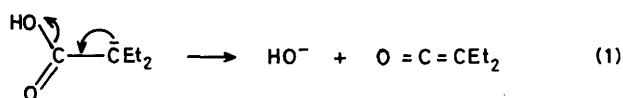


Figure. C.a. mass spectrum of the $(M - \text{D})^-$ ion from $\text{DO}_2\text{CCH}(\text{Et})_2$. Experimental conditions, see Experimental section. The width of major peaks at half height are: m/z (V) 99 (68.2), 86 (63.4), 71 (87.5), 55 (51.7), 44 (53.6), and 41 (51.0). When a voltage of 1 kV is applied 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)

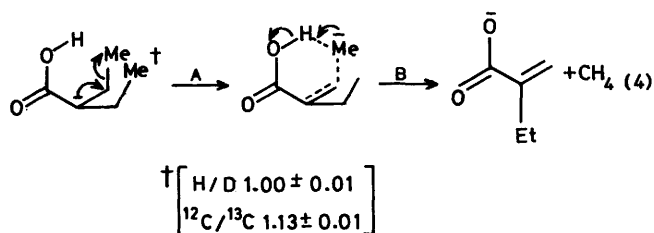
Table 3. C.a. and c.r. mass spectra of the acrylic acid ($M - H$)⁻ ion

C.a. m.s.: m/z (% loss); 70 (100, H⁺), 69 (15, H₂), 44 (48, C₂H₃⁺), 27 (28, CO₂)

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)



$$* \left[\begin{array}{l} \text{H/D } 1.25 \pm 0.02 \\ {}^{12}\text{C}/{}^{13}\text{C } 1.00 \pm 0.01 \end{array} \right]$$



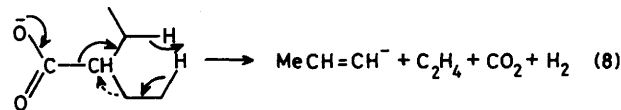
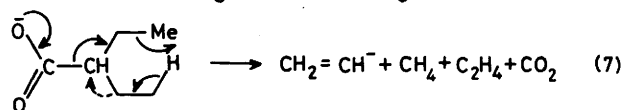
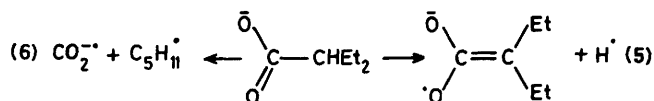
$$\dagger \left[\begin{array}{l} \text{H/D } 1.00 \pm 0.01 \\ {}^{12}\text{C}/{}^{13}\text{C } 1.13 \pm 0.01 \end{array} \right]$$

Scheme 1.

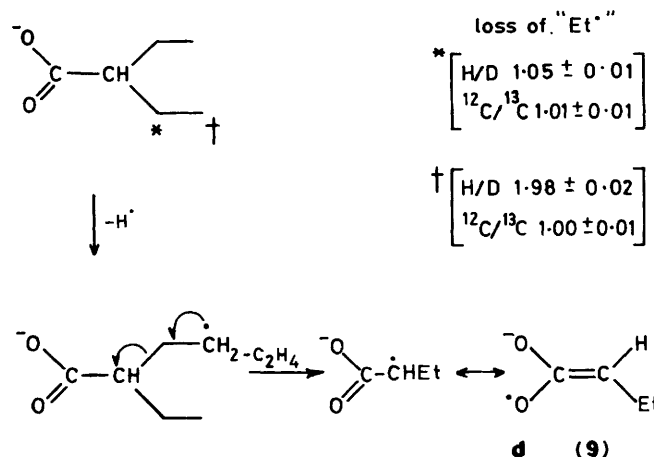
since the c.a. mass spectrum and charge-reversal (positive ion) mass spectrum³⁶ of m/z 71 and deprotonated acrylic acid are identical (see Table 3). The kinetic isotope effect [shown in equation (3)] favours a stepwise reaction in which the first step (incipient Me⁻ formation) is rate determining. (iv) 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) CO₂⁻ formation occurs from **a** [see equation (6)]; (iii) the ions C₂H₃⁻ (m/z 27) and C₃H₅⁻ (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

* The alternative reaction where H⁻ effects an S_Ni reaction to eliminate CO₂ and C₂H₆ seems a less likely possibility.

**Scheme 2.**

m/z 86 is formed by loss of the elements of C₂H₅⁻, 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 CD₃⁺ in the c.a. mass spectrum of Me(CD₃)CHCO₂⁻ is 1.1:1. Thus, the losses of Me⁺ and Et⁺ respectively from Me₂CHCO₂⁻ and Et₂CHCO₂⁻ 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 CO₂⁺⁺ (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 (CD₃CH₂)CHCO₂⁻ 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 Et₂CHCO₂⁻ originates from a methyl substituent (see above).

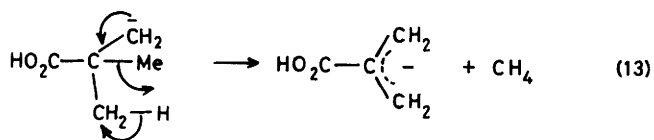
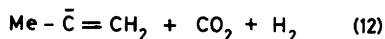
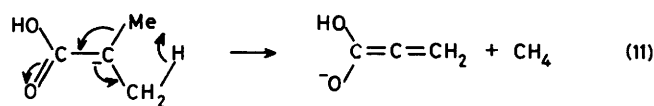
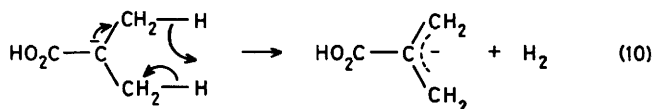
Table 4. C.a. mass spectra of carboxylate anions from (XI)—(XIV)

Anion	Loss									
	H ⁺	D ⁺	H ₂	HD	CH ₃ ⁺	CD ₃ ⁺	CH ₄	CH ₃ D	CD ₃ H	CD ₄
⁻ O ₂ CCHMe ₂	100		40		23		15			
⁻ O ₂ CCDMe ₂		100		32	20		14			
⁻ O ₂ CCH(CD ₃) ₂	100			35		19				10
⁻ O ₂ CCH(CD ₃)Me	100		22	12	10	9.5		7.5	8.0	
⁻ O ₂ CCMe ₃					92		78			

Anion	Formation										
	CO ₂ ⁻	C ₃ H ₅ ⁻	C ₃ H ₄ D ⁻	C ₃ H ₃ D ₂ ⁻	C ₃ H ₂ D ₃ ⁻	C ₃ D ₅ ⁻	C ₂ H ₃ ⁻	C ₂ H ₂ D ⁻	C ₂ HD ₂ ⁻	HO ⁻	DO ⁻
⁻ O ₂ CCHMe ₂	65	14					4			2	
⁻ O ₂ CCDMe ₂	62	12						3			2
⁻ O ₂ CCH(CD ₃) ₂	58					6			3	2	
⁻ O ₂ CCH(CD ₃)Me	68			8	<i>a</i>		2		1.5	2	
⁻ O ₂ CCMe ₃	100										

^a CO₂⁻ and C₃H₂D₃⁻ both 44 a.m.u.**Table 5.** C.a. and c.r. mass spectra of *m/z* 86 from Et₂CHCO₂⁻C.a. m.s., *m/z* (% loss): 85 (78, -H⁺), 71 (100, -Me⁺), 27 (2, -C₂H₃O₂⁻)C.r. (positive ion) m.s., *m/z* (%): 58 (12), 57 (14), 56 (16), 44 (42, CO₂⁺), 41 (72), 39 (100, C₃H₃⁺), 29 (82), 28 (66), 27 (92, C₂H₃⁺), 15 (12, CH₃⁺), 14 (8, CH₂⁺), 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 Me₂CHCO₂⁻ are similar to those of Et₂CHCO₂⁻, e.g. losses of H⁺ [cf. equation (5)], Me⁺ [cf. equation (5)], and the formation of CO₂⁻ [cf. equation (6)]. Some fragmentations are however quite different, viz. eliminations of H₂ [equation (10)], CH₄ [equation (11)], and the formation of C₃H₅⁻ [the atoms involved are shown in equation (12)].



In contrast, the pivalate anion Me₃CCO₂⁻ (Table 4) cannot eliminate H₂ since it cannot form an enolate ion, but loss of Me⁺ [cf. equation (5)] and the formation of CO₂⁻ [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 R₂CHCO₂⁻ (R = Me and Et) on collisional activation undergo proton transfer to yield the enolate ion R₂CCO₂H, and that both carboxylate and enolate ions undergo complex but characteristic fragmentations. When there is no hydrogen at

position 1 (as in Me₃CCO₂⁻) the enolate ion cannot be formed: in this case fragmentation occurs through both the carboxylate ion and ⁻CH₂(Me)₂CCO₂H.

Experimental

C.a. mass spectra and charge-reversal mass spectra³⁶ 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⁻) or from (I), (III), and (XII) by ²H abstraction by DO⁻ (or D⁻ or O⁻). Reactant negative ions were generated from either H₂O or D₂O by 100 eV electrons.³⁹ The indicated source gauge pressure (of H₂O or D₂O) 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 (²H₁ 98%).

Compounds (III) and (XII) were made by reduction of the α-bromo derivatives of (II) and (XI) using Zn-D₂O.⁴⁰

Compounds (V), (VII), (IX), and (X) were made from the reactions of butanoic acid with the commercially available MeCD₂I (²H₂ > 99%), CD₃CH₂I (²H₃ > 99%), Me¹³CH₂I (¹³C 91%), and ¹³CH₃CH₂I (¹³C 91%), using a modification of the method of Creger.⁴¹ Yields were 75–85%. The following example describes the method used.

2-[1,1-²H₂]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, [1,1-²H₂]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 (MgSO₄), and the solvent removed. The residual oil was distilled (85–100 °C at 13 mmHg) in a T tube to give 2-[1,1-²H₂]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 N₂ 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-[1,1-²H₂]Ethyl-[3,3-²H₂]butanoic Acid (IV).—(i) *Diethyl* [1,1-²H₂]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, [1,1-²H₂]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 (MgSO₄), and the solvent removed to give the product as an oil (242 mg, crude yield 87%).

(ii) *Diethyl di*-[1,1-²H₂]ethylmalonate. Crude diethyl [1,1-²H₂]ethylmalonate (242 mg) was converted into diethyl di-[1,1-²H₂]ethylmalonate (258 mg, crude yield 91%) by the method described in (i) above.

(iii) 2-[1,1-²H₂]Ethyl-[3,3-²H₂]butanoic acid (IV). A modification of the method of Krapcho was used.⁴²

Crude diethyl di-[1,1-²H₂]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 (MgSO₄), and the solvent removed to give crude ethyl 2-[1,1-²H₂]ethyl-[3,3-²H₂]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 (MgSO₄), 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-[²H₃]Methylpropanoic acid (XIV) was prepared from propanoic acid and [²H₃]methyl iodide by the method outlined above for (V). 2-[²H₃]Methyl-[3,3,3-²H₃]propanoic acid (XIII) was prepared from diethyl malonate by an identical procedure to that used for (IV) above.

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