Lactone Formation in Superacidic Media

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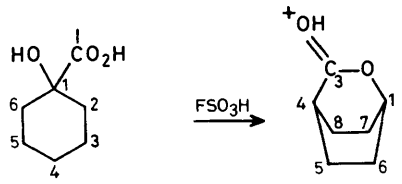
The reaction of substituted 1-hydroxycyclohexanecarboxylic acids in fluorosulphuric acid has been studied. Cyclisation takes place around 0 °C, accompanied by rearrangement in appropriate cases, yielding the thermodynamically stable lactone or mixture of lactones. An unexpected feature of these reactions is that the carboxy-substituted cyclohexyl carbocation does not undergo ring contraction, unlike the unsubstituted cyclohexyl carbocation, although the cycloheptyl system contracts to cyclohexyl. We suggest that the cyclohexyl carbocation is strongly stabilised by carboxyl substitution, as a result of through-space interaction between the carboxyl oxygen atom and the carbocation centre.

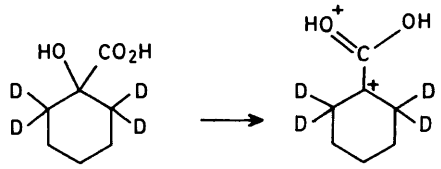
Superacidic media have long been recognised as ideal for carrying out cyclisation reactions.[1] Over the past decade, the method has been applied widely to obtain homocyclic and heterocyclic systems.[2] The work of Sorensen[3] on methylated linalools showed that the relative rates of competing methyl shift and carbocyclisation reactions were similar in superacidic and in normal acid media. The emphasis on cyclisation in superacids results from supression of competing reactions with external nucleophiles and elimination reactions; this allows intramolecular reaction of the carbocation with an internal nucleophile to dominate, yielding a cyclic product. Such a process usually yields the thermodynamically stable product, since the carbocation has a long lifetime under these conditions, and solvation by the counterion lowers barriers to rearrangement.[3]

Lactones should be readily accessible by this route, but the reaction has generally been ignored, except for formation in solution of the lactone of bicyclo[3.1.0]hex-2-ene-*endo*-6-carboxylic acid.[4] We have, therefore, investigated the preparation of lactones in superacidic conditions, starting with a simple example, cyclohexanecarboxylic acid 1,4-lactone (**1**). Our experience of superacid reactions has been that the carbocation centre is relatively mobile, so that in this case a carbocation generated at any convenient position should migrate to give the stable 1,4-lactone. We therefore took the readily accessible 1-hydroxycyclohexanecarboxylic acid (**2**), and dissolved it in FSO_3H–SO_2 at −70 °C. The ^{13}C n.m.r. spectrum showed only the presence of the protonated acid. On warming the solution to 0 °C overnight, and then adding fresh SO_2 and running the spectrum at −70 °C, the presence of the lactone (**1**) was detected. Quenching the reaction mixture in alkaline aqueous methanol gave the lactone as a crystalline solid, whose identity was confirmed conventionally.



(**2**) (**1**)

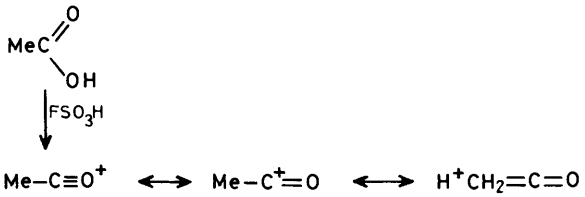
Migration of the carbocation from C-1 to C-4 could take place either directly in a 1,4-shift, or by a combination of 1,2- and possibly 1,3-shifts. To distinguish between the possibilities, we repeated the experiment on a sample of (**2**) which had been fully deuteriated on C-2 and C-6. The deuteriated sample in FSO_3H–SO_2 at −70 °C gave a spectrum similar to that of the undeuteriated acid in similar conditions except for loss of the C-2 peaks. On warming to −10 °C, the spectrum was unchanged. However, on standing at 0 °C overnight, a ^{13}C spectrum was obtained which was consistent with the formation of (**3**).



(**2a**) (**3**)

Clearly, deuteriation of C-2 blocks the hydride shift, which must, therefore, start with a 1,2-shift. Unexpectedly, (**3**) is sufficiently stable that (**1**) is not formed.

Although the obvious route for formation of (**3**) from protonated (**2a**) is by further protonation and ionisation, we have no evidence to support a diprotonated substrate, and an alternative route exists. Olah[5] has shown that carboxylic acids cleave at around −10 °C in superacidic media to give acyl cations which exist as resonance hybrids.



No evidence for the existence of such a species was found in our work; Olah reported a characteristic peak of the *sp* hybrid carbon at about 40 p.p.m. upfield of the position of the peak from the same carbon in the unprotonated acid which is absent in our spectra. Such an intermediate could rearrange rapidly to a species such as (**3**) if formed in a hydroxy acid, and our work offers no distinction between the two routes.

Since this experiment clearly shows that migration of the carbocation round the ring proceeds stepwise, it should be possible to modify the course of the reaction by substituting the ring at positions 2 or 3, giving rise, possibly, to 1,2- or 1,3-lactones by stabilising the positive charge at one of these positions.

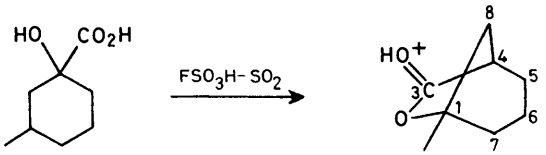
A solution of 1-hydroxy-3-methylcyclohexanecarboxylic acid (**4**) in FSO_3H–SO_2 at −70 °C gave a spectrum of the pro-

Table. ^{13}C N.m.r. chemical shifts (p.p.m. from Me_4Si) in FSO_3H–SO_2

Compd.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-1′	
(1)	94.6		203	35	25.7*	26.8*	26.8*	25.7*		
(2)	81.0	33.9	21.0	21.8	21.0	33.9			200.0	
(3)	326	40	30.5	24.4	30.5	40			259.5	
(5)	116		203	46.6	26.4	19.8	33.2	44		Me on C-1 25.8
(7)	94		200	40.6	26	31.8	31.8	26		Me on C-4 19
(8)	103		204	40.9	33	21*	25*	26*		Me on C-5 11
(9)	?	?	?	229	151	259			202	Me on C-6 21
(11)	119		200.5	37	25	34	23	34.5		

* Assignments could be interchanged.

tonated acid only. The spectrum was initially unchanged on warming the sample to −30 °C, but on maintaining it at this temperature for a week, the spectrum changed to that of the protonated 1,3-lactone (**5**).

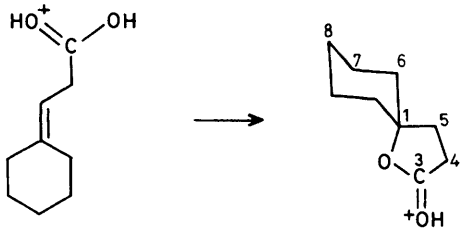


(**4**) (**5**)

On warming the solution of (**5**) to 25 °C, the lactone decomposed over a period of three days, giving a species which we were unable to identify from its spectrum.

The ^{13}C n.m.r. spectrum of a solution of 1-hydroxy-2-methylcyclohexanecarboxylic acid (**6**) in FSO_3H–SO_2 at −70 °C showed the presence of two species, one of which is the protonated acid, the other an unidentified species with shifts characteristic of an allylic carbocation. On warming to −20 °C overnight, the latter species decomposes, leaving only the protonated acid. On further warming to 0 °C overnight, the protonated acid decomposes to form three species, (**7**), (**8**), and (**9**); possible routes to these species are suggested below. Identification of (**9**) is provisional, as we were unable to positively identify the CH_2 peaks. The oxidation required to form (**9**) is uncommon, though not unprecedented,[6] particularly at the temperature at which this reaction is carried out.

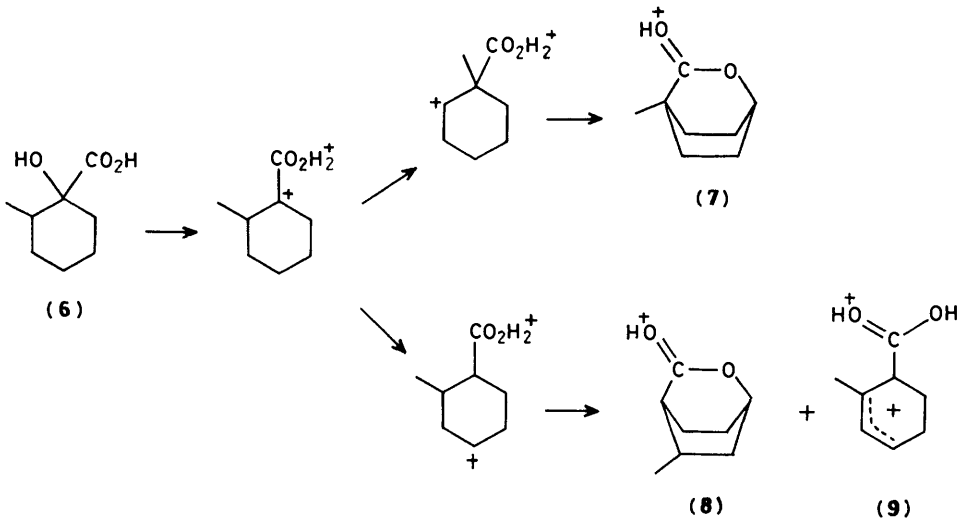
this is not of importance in this work, but could be significant if less stable substrates are cyclised. Ionisation of the 1-hydroxy group is presumably inhibited by the neighbouring protonated carboxyl group, so we attempted to carry out reaction *via* the alkene, as used previously.[4] In FSO_3H–SO_2 at −70 °C β-cyclohexylidenepropionic acid (**10**) reacted rapidly to form the spiro-lactone (**11**).



(**10**) (**11**)

Attempts to repeat the preparation of (**1**) by dissolving cyclohex-3-enecarboxylic acid in FSO_3H–SO_2 at −70 °C were not successful. Reaction took place immediately to give an ionic species which has not been identified, though it has a spectrum similar to that of (**1**).

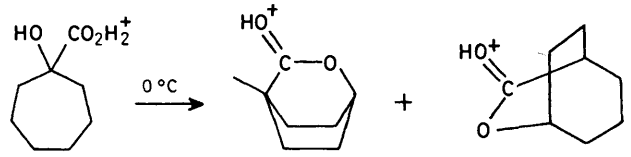
A surprising, and unexplained, feature of these reactions is the failure of the cyclohexane ring to undergo ring-contraction reactions. Rapid ring contractions of the secondary cyclohexyl cation[7] and of the chloro-substituted ion[8] have prevented observation of the parent ions; ring contraction is also reported to be rapid in the gas phase.[9] Our carboxy-substituted ion,



which should be less stable than the unsubstituted ion, does not undergo this reaction at 0 °C, but instead favours cyclisation to the bicyclic lactone, a process which involves an initial flipping

In all the substrates studied to date, ionisation of the tertiary hydroxy group takes place at relatively high temperatures. Since the lactones involved are stable in superacidic conditions

of the chair form of the cyclohexane ring into the boat form, which has a fairly high energy barrier. To see if ring contraction is a viable process in carboxylic acid substrates, we dissolved 1-hydroxycycloheptanecarboxylic acid (**12**) in FSO_3H–SO_2 at −70 °C, and obtained the ^{13}C n.m.r. spectrum of the protonated acid. This species was stable at −20 °C overnight, but on leaving at 0 °C overnight it reacted to yield mainly 1-methylcyclohexanecarboxylic acid 1,4-lactone (**7**) together with small amounts of the unrearranged lactone (**13**).



(**12**) (**7**) (**13**)

Clearly, ring-contraction reactions do take place, following the direction predicted,[10] consistent with reaction *via* protonated cyclopropane intermediates.[7] The ring contraction is not, then, inhibited by the presence of the protonated carboxy group in the substrate.

The reason for inhibition of the cyclohexyl to cyclopentyl ring contraction remains obscure. A possible explanation is that the bicyclic cyclohexyl lactones are thermodynamically more stable than bicyclic cyclopentyl lactones; this must be rejected, since equilibration of the ions before bicyclisation would be expected to involve scrambling of the deuterium label in (**2a**) or equilibration of methyl substituents in (**4**) and (**6**)

Alternatively, it could be argued that the cyclohexyl cation is not normally formed, and the hydroxy group is lost as a result of displacement by the carboxy group to give an α-lactone, which then undergoes stepwise ring expansion. However, such an argument appears equally applicable to the cycloheptyl system, where ring contraction is observed, and does not explain the failure of β-cyclohexylidenepropionic acid (**10**) to undergo ring contraction during reaction. Clearly, the presence of the carboxyl group is increasing the stability of the cyclohexyl ion; an ion formed on C-1 would be destabilised by electron-withdrawal, and migrate rapidly to C-2 by hydrogen or methyl shift. At this point, a thorough-space interaction with the oxygen of the carboxy would provide sufficient stabilisation to avoid ring contraction. In the case of the cycloheptanecarboxylic acid carbocation, the distance between the carbocation centre on the more distant carbon atoms would minimise the interaction, and permit ring contraction to the 1-carboxy-4-methylcyclohexenium ion. The β-cyclohexylidenepropionic acid would yield an ion on C-1 in which interaction was possible, and would hence cyclise without rearrangement.

Experimental

^1H N.m.r. spectra were recorded on a Perkin-Elmer R34 (220 MHz) spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Decoupling experiments were carried out on a Bruker WM250 (250 MHz) spectrometer operating in the Fourier transform mode. ^{13}C N.m.r. spectra were recorded on a Varian X-L 100 (25.2 MHz) spectrometer with $CDCl_3$ as solvent and $SiMe_4$ as internal standard for neutral solutions and sulphur dioxide or sulphuryl chloride fluoride as solvent for superacidic solutions with an external deuterium lock of [$^2H_6$]acetone or [$^2H_4$]methanol and external standard of $SiMe_4$ enclosed within a 5 mm n.m.r. tube.

I.r. spectra were recorded on a Perkin-Elmer 1320 i.r. spectrometer using either liquid films or Nujol mulls. Mass spectra were recorded on an A.E.I. MS 12 spectrometer. Accurate mass and g.l.c.–mass spectral analysis were recorded on a VG 7070E mass spectrometer.

Reaction mixtures were analysed by Perkin-Elmer F17 and Dani 3800 gas–liquid chromatographs with flame ionisation detectors using nitrogen as the carrier gas. The F17 instrument employed a 5 ft stainless steel column of 2 mm internal diameter using 10% OV351 on Celite as support material. The 3800 instrument employed a 25 m capillary column with 0.3 mm internal diameter and coated with OV351.

1-*Hydroxycyclohexanecarboxylic Acid* (**2**).—A solution of sodium metabisulphite (4.84 g, 0.025 mol) in distilled water (20 ml) was added over 0.5 h to a stirred mixture of cyclohexanone (4 g, 0.041 mol), potassium cyanide (3.3 g, 0.051 mol), and water (20 ml). This mixture was kept at 25 °C for two h. Ether extraction, drying, and removal of solvent gave α-hydroxycyclohexanecarbonitrile. The carbonitrile (2 g, 0.018 mol) was then refluxed with glacial acetic acid (30 ml) and concentrated HCl (30 ml) for three h. After this time, the solution was concentrated *in vacuo*. The residue was dissolved in chloroform, washed with water, and extracted with sodium hydrogen carbonate solution. This was separated, acidified with concentrated HCl, and extracted with chloroform. The chloroform extracts were dried and concentrated *in vacuo* to give a white solid (1.9 g, 32%) which was recrystallised from n-hexane, m.p. 105 °C (lit.,[11] 106—107 °C); *m/z* 99 (−CO_2H); δ([$^2H_6$]acetone) 1.2—2.0 (10 H, m, CH_2) and 5—6 (1 H, br s, OH); $\nu_{max.}$ (cm^{-1}) 3 500—2 500, 1 700, 1 430, and 1 300.

1-*Hydroxy*-3-*methylcyclohexanecarboxylic Acid* (**4**).—This was prepared from 3-methylcyclohexanone (11.2 g, 0.1 mol), potassium cyanide (8.5 g, 0.13 mol), and sodium metabisulphite (12.35 g, 0.12 mol) as previously described. The acid was recrystallised from n-hexane (3.5 g, 23%), m.p. 95—100 °C; *m/z* 113 (−CO_2H); δ 1.87 (3 H, d, Me), 1.4 (1 H, t, C*H*), 1.68 (6 H, br s, CH_2), 1.8 (1 H, m, C*H*Me), and 1.6 (1 H, d, C*H*H); $\nu_{max.}$ (cm^{-1}) 3 500—2 500, 2 900, 1 700, 1 450, 1 250, and 1 025.

1-*Hydroxy*-2-*methylcyclohexanecarboxylic Acid* (**6**).—This was prepared from 2-methylcyclohexanone (4.4 g, 0.0392 mol) as previously described. The acid was recrystallised from n-hexane (1.3 g, 21%), m.p. 95—100 °C; *m/z* 113 (−CO_2H); δ 0.85 (3 H, d, Me) and 1.3—1.8 (9 H, m, CH_2 and CH); $\nu_{max.}$ (cm^{-1}) 3 500—2 500, 2 900, 1 700, 1 450, 1 220, 1 150, and 750.

1-*Hydroxycycloheptanecarboxylic Acid*[12] (**12**).—This was prepared from cycloheptanone (4.4 g, 0.04 mol) as previously described. The acid was recrystallised from n-hexane (1.2 g, 19%), m.p. 82—83 °C; *m/z* 113 (−CO_2H); δ 1.6 (6 H, br s, CH_2), 1.7 (2 H, t, CH_2), 1.78 (2 H, t, CH_2), 2.0 (2 H, dd, CH_2), and 7.0 (1 H, br s, OH); $\nu_{max.}$ (cm^{-1}) 3 300—2 500, 2 900, 1 700, 1 450, 1 380, 1 270, 1 180, and 1 060.

[2,2,6,6-$^2H_4$]*Cyclohexanone*.—Cyclohexanone (5 g, 0.05 mol) was stirred for two days in a sealed flask containing D_2O (50 ml) to which sodium (0.5 g) had been added. After this time the cyclohexanone was separated and retreated with a fresh batch of D_2O for a further three days. The cyclohexanone was again separated by pentane extraction, dried, and distilled, b.p. 153 °C (4.1 g, 82%). G.l.c. showed >99% purity, *m/z* 103; δ 1.7 (2 H, m, CH_2) and 1.8 (4 H, m, CH_2); $\nu_{max.}$ (cm^{-1}) 2 940, 2 860, 2 230, 1 800, 1 250, and 1 130.

1-*Hydroxy*[2,2,6,6-$^2H_4$]*cyclohexanecarboxylic Acid* (**2a**).—This was prepared from the deuteriated ketone as previously described, (2 g), m.p. 106—108 °C; *m/z* 148; δ 1.3 (1 H, m, CH), 1.45 (1 H, m, CH), and 1.5—1.6 (4 H, m, CH_2); $\nu_{max.}$ (cm^{-1}) 3 500—2 500, 2 230, 1 730, 1 450, 1 380, and 730.

β-*Carboxyethyltriphenylphosphonium Chloride*.—Triphenylphosphine (13.1 g, 0.05 mol) and 3-chloropropionic acid (5.4 g, 0.05 mol) were heated at 150 °C for two h. After cooling, the resulting crystalline mass was dissolved in absolute ethanol. Addition of ether, with stirring, gave the phosphonium salt (12.5 g), m.p. 195 °C (lit.,[13] 196—198.5 °C); *m/z* 369; δ 2.75 (2 H, p, CH_2CO_2H), 3.75 [2 H, p. $CH_2P(Ph)_3$], and 7.7—7.8 (15 H, m, Ph); $\nu_{max.}$ (cm^{-1}) 3 200—2 500, 2 900, 1 700, 1 450, 1 375, 1 220, 1 100, 730, and 680.

β-*Cyclohexylidenepropionic Acid* (**10**).—A mixture of β-carboxyethyltriphenylphosphonium chloride (14 g, 0.038 mol) and cyclohexanone (3.7 g, 0.038 mol) in DMSO–THF (100 ml) (50:50) was added to an ice-cooled solution of sodium hydride oil dispersion (3.6 g, 0.15 mol) in DMSO–THF (50 ml) (50:50) under nitrogen. After six h the reaction was ended by addition of water and acidification. Ether extraction and concentration gave an amber oil which was distilled to give the pure acid (1.6 g, 28%), b.p. 120 °C at 0.5 Torr (lit.,[14] 105 °C at 0.35 Torr). This solidified on standing to give a clear crystalline solid, m.p. 32—36 °C; *m/z* 154; δ 1.52 (6 H, br s, CH_2), 2.12 (4 H, br s, CH_2C–), 3.08 (2 H, d, CH_2CO_2H), and 5.25 (1 H, t, =CH); $\nu_{max.}$ (cm^{-1}) 3 500—2 500, 2 900, 1 700, and 1 450.

Generation of Carbocations.—Sulphur dioxide (1 ml) was condensed into a 10 ml round-bottom flask cooled in dry ice–ethanol mixture, and fluorosulphuric acid (2 ml) added. A solution of the substrate (250—500 mg) in sulphur dioxide (1 ml) at −78 °C (when solution was incomplete, the acid was added as a suspension) was added dropwise with stirring. The spectrum of the solution was then recorded on a Varian X-L 100 spectrometer with an external lock of [$^2H_6$]acetone in a sealed tube.

Quenching of the Lactone Derived from 1-*Hydroxycyclohexanecarboxylic Acid in* FSO_3H.—A solution of 1-hydroxycyclohexanecarboxylic acid (5 g) and FSO_3H (15 ml) in SO_2 was prepared by very slow addition of the cooled solid to the FSO_3H–SO_2 solution cooled in dry ice–alcohol, since the acid was sparingly soluble in SO_2. After evaporation of the SO_2 and standing overnight at 0 °C, the solution was dripped slowly into a rapidly stirred cooled slurry of potassium carbonate (50 g) in aqueous methanol (500 ml). After warming to room temperature, the aqueous solution was continuously extracted with chloroform for 15 h. Concentration of the chloroform solution gave the lactone (1 g) as a white solid, m.p. 112—118 °C; *m/z* 126. The ^1H n.m.r. spectrum had 4.75 (1 H, br s, CHO), 2.68 (1 H, br s, C*H*CHO), and 1.75—2.1 (8 H, m, CH_2). The yield of lactone is unexpectedly low, since a very clean spectrum was obtained; we suggest that the extraction procedure was probably inadequate for efficient recovery of the material.

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