The Formation of Glutaric and Succinic Acids in the Oxidation of Cyclohexanol by Nitric Acid

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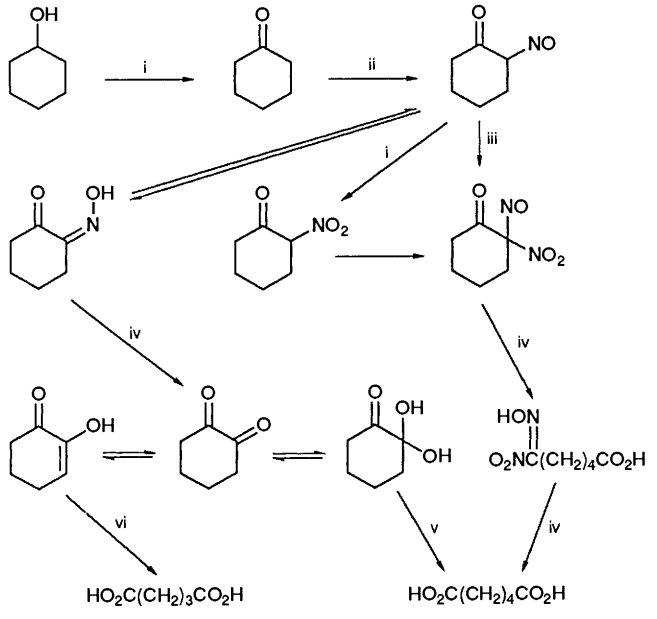
The yields of the dibasic acid products from the oxidation of 2,2-dimethylcyclohexanol, 4-methylcyclohexanol and a mixture of cyclohexanol and [1-^{14}C]cyclohexanone by nitric acid at 73 °C have been measured. The influence of copper(II) and of vanadium(V) catalysts on the product distributions has also been investigated. The data show that in the oxidation of cyclohexanol to adipic acid the by-product glutaric acid arises predominantly by the loss of C-2 rather than C-1 and succinic acid from the loss of C-2 with C-3. The results are used to identify possible mechanisms leading to the lower dicarboxylic acids. These are investigated further by examining the oxidation products from probable intermediates and from related compounds. These studies lead to the conclusion that the intermediate 2-nitrosocyclohexanone undergoes competing reactions that lead to adipic acid or glutaric and succinic acid.

The oxidation of cyclohexanol or mixtures of cyclohexanol and cyclohexanone by nitric acid, in the presence of catalytic amounts of vanadium(V) and copper(II) salts, is the preferred method used for the manufacture of adipic acid,[1] the critical intermediate in the production of nylon 6,6. In the absence of the catalysts adipic acid is formed in typically $<80\%$ yield with significant quantities of lower dicarboxylic acids, principally glutaric and succinic acids, also being found. The major role of the catalysts is to enhance the yield of adipic acid to 90–95% at the expense of these lower dicarboxylic acids.[2]

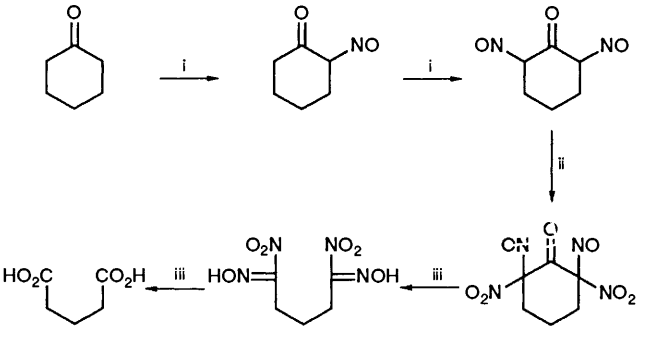
This important oxidation has been the subject of many studies[3] one of the earliest of which is described in a technical report captured by allied forces at the end of the second world war.[3a] These investigations reveal a complex mechanism involving several intermediates in parallel and competing processes. Although all the steps have not been clearly defined, an overall scheme that describes a consensus view of the major routes to adipic acid is given in Scheme 1.



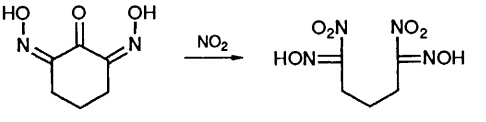
Scheme 1 *Reagents:* i, HNO_3, $-HNO_2$; ii, HNO_2; iii, HNO_3; iv, H^+, H_2O; v, V^V; vi, HNO_3, V^V

The lower dicarboxylic acid by-products arise from alternative reactions of one or more of the intermediates in Scheme 1 and not from further oxidation of adipic acid.[3c,j]

One route that has been proposed for the formation of glutaric acid involves 6-nitrosation of 2-nitrosocyclohexanone[3a,g,i] with subsequent reaction and loss of C-1 as CO_2 (Scheme 2). Consistent with this mechanism 2,6-dihydroxyiminocyclohexanone, a tautomer of 2,6-dinitrosocyclohexanone, reacts with nitrogen dioxide to give 1,5-dihydroxyimino-1,5-dinitropentane[3a] (Scheme 3). An alternative route to glutaric acid, which we proposed in an earlier paper, involves vanadium(V) catalysed oxidation of the mono-enol of cyclohexane-1,2-dione.[4] In contrast to the first pathway this should lead to loss of C-1 or C-2 in equal amounts (Scheme 4).



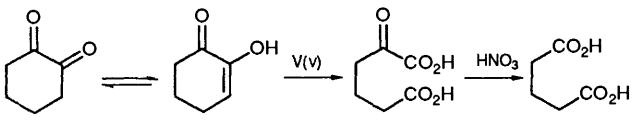
Scheme 2 *Reagents:* i, HNO_2; ii, HNO_3; iii, H^+, H_2O



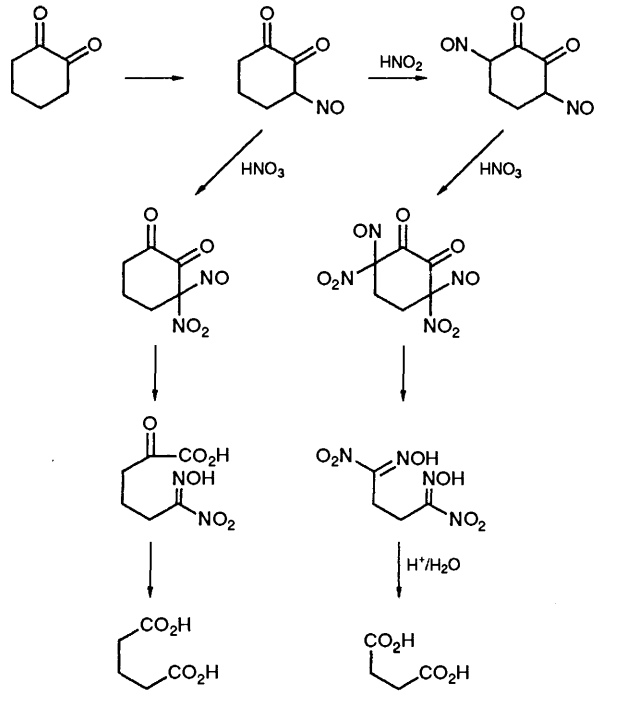
Scheme 3

In a third possible oxidation, it has been suggested that mono- and di-nitrosation of cyclohexane-1,2-dione could lead to glutaric and succinic acids, respectively (Scheme 5).[3a,b] In agreement with the latter reaction the nitric acid oxidation of the dione is reported to give succinic and oxalic acids.[3a,j] This mechanism would lead to succinic acid with the loss of C-1 and C-2 as oxalic acid, whereas the glutaric acid, like that arising from the vanadium(V) oxidation of cyclohexane-1,2-dione in Scheme 4, would involve an equal chance of losing either C-1 or C-2.

Our continued interest in the nitric acid oxidation of cyclohexanol to adipic acid has led us to investigate the reactions leading to the by-products glutaric and succinic acids.



Scheme 4



Scheme 5

Table 1 Product yields from the oxidation of cyclohexanol and 2,2-dimethylcyclohexanol by nitric acid at 73 °C[a]

Substrate	Metal ion Cu^{II}	Metal ion V^{V}	Yield of dicarboxylic acid (%) Succinic	Glutaric	Adipic	Total
OH	–	–	6.5	13.1	78.5	98.1
	+	+	1.7	3.7	94.6	100.0
	+	–	4.4	3.6	90.9	98.9
	–	+	4.2	10.5	83.4	98.1
			Yield of 2,2-dimethyldicarboxylic acid (%)[b]			
			Succinic	Glutaric	Adipic	Total
OH, Me, Me	–	–	4.4	24.6	47.9	76.9
	+	+	4.0	8.0	84.5	96.5
	+	+[c]	0.6	4.4	93.0	98.0
	+	–	4.3	24.4	57.6	86.3
	–	+	5.2	12.6	80.6	98.4

[a] Conditions: substrate (0.01 mol), 55% w/w nitric acid (20 cm^3), copper(II) nitrate 0.22% w/w and ammonium metavanadate 0.05% w/w in the nitric acid where appropriate. [b] Products 2,2-dimethylsuccinic, 2,2-dimethylglutaric and 2,2-dimethyladipic acid. Substrate 5.0×10^{-3} mol in 55% w/w nitric acid (10 cm^3). [c] 1% ammonium metavanadate.

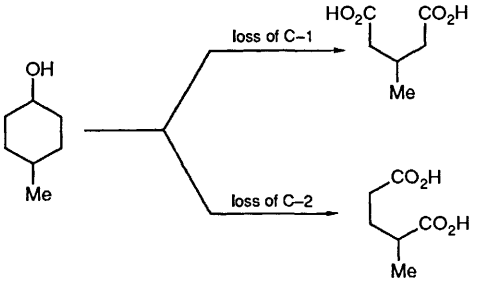
In this paper we report the results of these studies, suggest the most likely pathways to the lower dicarboxylic acids and discuss the role of the catalysts in minimising the formation of these compounds.

Results and Discussion

The reactions were carried out on a small scale at 73 °C using nitric acid (55% w/w) under four distinct regimes: (i) in the absence of catalysts, (ii) in the presence of copper(II) nitrate and ammonium metavanadate, (iii) in the presence of copper(II) nitrate and (iv) in the presence of ammonium metavanadate. The reaction protocol was described in our previous paper.[4]

We argued that if the formation of glutaric and succinic acids in the oxidation of cyclohexanol involves 6-nitrosation and loss of C-1 (Schemes 2 and 5), 2,2-dimethylation of the substrate should block these pathways. Table 1 records the product yields from the oxidation of cyclohexanol and its 2,2-dimethylated derivative under the four regimes. The results show that both substrates give similar yields of dicarboxylic acids. More importantly, 2,2-dimethylation of cyclohexanol clearly does not lead to a decrease in the yields of the lower dicarboxylic acid by-products with a corresponding increase in the 2,2-dimethyl adipic acid. Indeed, for each oxidation regime, the yield of the 2,2-dimethylglutaric acid is significantly higher for the dimethylated substrate than glutaric acid from cyclohexanol. Assuming both substrates react by the same mechanism, the results indicate that the formation of neither glutaric nor succinic acid requires the oxidative loss of C-1 from cyclohexanol.

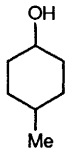
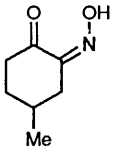
The mechanistic conclusions above were investigated further by using 4-methylcyclohexanol as the substrate. This cyclohexanol derivative was selected to minimise the effect of the substituent on the course of the reaction, since it could have been argued that the methyl groups in 2,2-dimethylcyclohexanol might, through their close proximity to the alcohol group, have had a significant influence on the mechanism of the oxidation. By contrast, the 4-methyl group in 4-methylcyclohexanol should cause a much smaller disturbance to the reaction mechanism and in effect act as a label. The oxidative loss of C-1 would give 3-methylglutaric acid whilst that of C-2 would result in the formation of 2-methylglutaric acid (Scheme 6).



Scheme 6

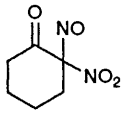
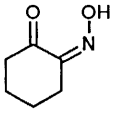
The oxidation of 4-methylcyclohexanol by nitric acid in the absence of copper(II) and vanadium(V) ions has been reported previously by two groups.[3m,5] Although they used very similar reaction conditions their product distributions were markedly different (Table 2). We reinvestigated the oxidation in the absence of catalysts and also carried out the reaction under the three other regimes. Our results (Table 2), which compare well with those from cyclohexanol (Table 1), differ from the comparable data from the earlier work with 4-methylcyclohexanol, although they are closer to those of Sojka *et al.*[3m] than those of Lubyanitskii and his co-workers.[5] The effects of the catalysts are essentially the same for both substrates. Thus, copper(II) diverts most of the glutaric acid products to adipic acid whilst vanadium(V) is responsible for a somewhat smaller change in the product distribution. The largest differences between the two substrates occur for reactions in the absence of copper(II), although the precise cause for these is unclear. The results in Table 2 show that, in the absence of the catalysts, the major pathway to glutaric acids involves the oxidative loss of C-2 with a very small amount arising from the loss of C-1. This is in

Table 2 Product yields from the oxidation of 4-methylcyclohexanol and 4-methyl-2-hydroxyiminocyclohexanone by nitric acid[a]

Substrate	Metal ion		Yield of dicarboxylic acid (%)					
	Cu^{II}	V^{V}	Succinic	Methylsuccinic	2-Methylglutaric	3-Methylglutaric	3-Methyladipic	Total
	–	–[b]	0	1.5	8.1	0.2	83.4	93.2
	–	–[c]	1.3	0	0	1.4	83.4	86.1
	–	–	2.2	1.6	16.3	0.6	68.6	89.3
	+	+	0.7	0.1	2.8	1.6	92.9	98.1
	+	–	0.7	1.7	2.4	1.0	89.0	94.8
	–	+	3.1	0.1	18.0	0.9	72.4	94.5
	–	–	1.3	5.3	0.6	2.1	83.6	92.9
	+	+	0.5	0.2	0.5	3.8	93.6	98.6
	+	–	0.5	5.0	0.4	2.4	83.4	91.7
	–	+	0.6	0.3	0.5	3.0	94.0	98.7

[a] Conditions: see Table 1. [b] From ref. 3(*m*). [c] From ref. 5.

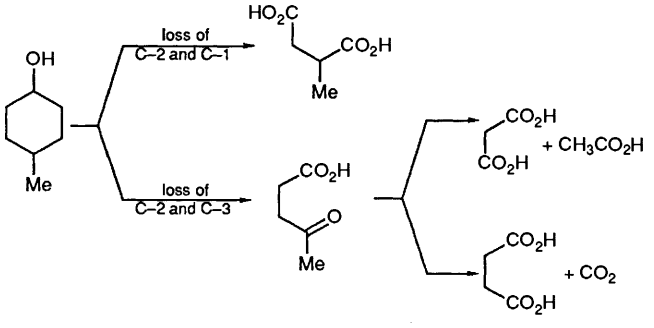
Table 3 Yields of products from the nitric acid oxidation of 5-oxohexanoic, 6-oxoheptanoic, 6-oxohexanoic, 6-hydroxyiminohexanoic and 6-nitro-6-hydroxyiminohexanoic acids and 2-nitro-2-nitrosocyclohexanone and 2-hydroxyiminocyclohexanone[a]

Substrate	Metal ions		Yield of products (%)					
	Cu^{II}	V^{V}	Acetic	Succinic	Glutaric	Adipic	CO_2	Total
$HO_2C(CH_2)_3COCH_3$	+	+	62.8	62.6	34.2	0	33.9	96.4
$HO_2C(CH_2)_4COCH_3$	–	–	—	14.8	64.5	20.9	—	100.2
	+	+	—	2.3	77.9	19.6	—	99.8
	+	–	—	10.3	68.1	19.8	—	98.2
	–	+	—	6.2	73.1	22.1	—	101.4
$HO_2C(CH_2)_4CH{=}NOH$	–	–	—	19.6	47.5	17.8	—	84.9
	+	+	—	19.5	58.3	20.1	—	97.9
$HO_2C(CH_2)_4CHO$	–	–	—	13.4	56.1	16.7	—	86.2
	+	+	—	12.2	68.3	16.1	—	96.6
$HO_2C(CH_2)_4C(NO_2){=}NOH$	–	–	—	<0.2	0.8	99.4	—	100.2
	+	+	—	<0.2	<0.2	99.9	—	99.9
	–	–	—	<0.2	0.3	99.0	—	99.3
	+	+	—	<0.2	0.5	98.0	—	98.5
	–	–	—	5.8	1.8	86.0	—	93.6
	+	+	—	1.1	5.0	93.1	—	99.2
	+	–	—	4.9	3.5	84.6	—	93.0
	–	+	—	0.6	3.1	92.7	—	96.4

[a] Conditions: see Table 1.

agreement with the product distribution from 2,2-dimethylcyclohexanol. The presence of copper(II) dramatically reduces the oxidative loss of C-2 but has no effect on the reaction involving loss of C-1. By contrast vanadium(v) has little effect on the yield of the glutaric acids.

The oxidation of 4-methylcyclohexanol gives both 2-methylsuccinic and, somewhat unexpectedly, succinic acid. These compounds must arise by oxidative loss of C-1 with C-2 and C-2 with C-3, respectively. We propose that the latter oxidation occurs *via* the initial formation of 4-oxopentanoic acid (Scheme 7) which reacts further to give either succinic acid with CO_2 or malonic with acetic acid. The malonic, being a 1,3-dicarboxylic acid, would be expected to decarboxylate under the reaction conditions. This mechanistic scheme is supported by the products from the oxidation of the homologues, 5-oxohexanoic and 6-oxoheptanoic acid. In the oxidation of the oxohexanoic



Scheme 7

acid all the carbon-containing products were quantified (Table 3). The results show that the carbon balance is close to 100%

Table 4 The percentage retention of C-1 from 4-methylcyclohexanol in the products from nitric acid oxidation

Metal ion		Percentage retention of C-1 (yield %)	
Cu^{II}	V^{V}	Succinic acids[a]	Glutaric acids[b]
–	–	75 (3.8)	96 (16.9)
+	+	95 (0.8)	64 (4.4)
+	–	80 (2.4)	71 (3.4)
–	+	97 (3.2)	95 (18.9)

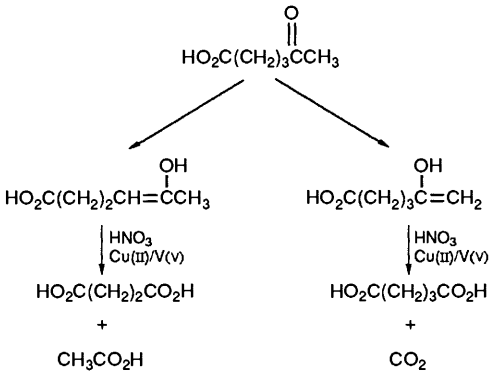
[a] Includes succinic and 2-methylsuccinic acid. [b] Includes 2- and 3-methylglutaric acid.

Table 5 The percentage retention of ^{14}C in glutaric and succinic acid from the oxidation of a mixture of cyclohexanol and [1-^{14}C]cyclohexanone by nitric acid[a]

Metal ions		% Yield of $HO_2C(CH_2)_nCO_2H$ (^{14}C retention, %)[b]			
Cu^{II}	V^{V}	$n = 2$	$n = 3$	$n = 4$	Total
–	–	6.8 (89)	12.9 (101)	77.9 (100)	97.6
+	+	1.8 (71)	4.4 (100)	93.4 (100)	99.6
+	–	3.8 (70)	4.2 (91)	89.7 (100)	97.7
–	+	7.9 (77)	17.8 (97)	73.4 (100)	99.1

[a] Conditions: 9:1 w/w cyclohexanol: [1-^{14}C]cyclohexanone, see Table 1. [b] Percentage retention of ^{14}C relative to ^{14}C in adipic acid.

and, from the product distribution, it is clear that the acetic acid is formed in conjunction with the succinic acid and the carbon dioxide in parallel with the glutaric acid. These results can be explained, assuming oxidation occurs by two competing pathways, as shown in Scheme 8. The major route leads *via* the more



Scheme 8

stable enol to succinic acid. With 6-oxoheptanoic acid the corresponding reactions would give acetic with glutaric acid and adipic acid with carbon dioxide. The succinic acid, that is a significant product in the absence of vanadium(v), must arise from an alternative oxidation that competes with the process above when the catalyst is omitted.

The yields of the glutaric and of the succinic acids from the oxidation of 4-methylcyclohexanol can be used to calculate the % retention of C-1 from the substrate under the different regimes (Table 4).

Although the oxidation of 4-methylcyclohexanol and of 2,2-dimethylcyclohexanol both show glutaric acids are formed preferentially by loss of C-2, there are some distinct differences between the influence of the catalysts on the two oxidations. Thus for 4-methylcyclohexanol, like cyclohexanol, the presence of copper(II) is important to minimise the formation of glutaric acids and vanadium(v) has a marginal effect, whilst for 2,2-dimethylcyclohexanol the reverse is true. The causes of these differences are unclear, however, it does suggest that the proximity of the methyl groups to the hydroxyl in 2,2-dimethylcyclohexanol has a pronounced effect on the mechanism of the oxidation.

Although the product distributions from the oxidation of cyclohexanol and of 4-methylcyclohexanol are very similar, it is possible that the 4-methyl group could affect the preferred conformations of the cyclohexane ring and consequently influence the reaction mechanism. Consistent with this possibility is the report by Druliner[6] that a 4-methyl group has a substantial effect on the cobalt(III)/oxygen oxidation of cyclohexanone. In this case, with 4-methylcyclohexanone the ratio of 3-methylglutaric to 2-methylglutaric acid (loss of C-1 to C-2) was 3:1. This preferred loss of C-1 was in contrast to that observed with [1-^{14}C]cyclohexanone where C-2 loss accounted for >90% of the glutaric acid. The difference was attributed to a steric effect of the methyl group.

As a final test of the origin of the carbon atoms lost in the oxidation of cyclohexanol to glutaric and succinic acid we have examined the reactions of [1-^{14}C]cyclohexanone with nitric acid for which there can be no conformational or steric differences from those of cyclohexanone. We selected the labelled ketone rather than the corresponding alcohol to simplify the preparation of the starting material and we carried out the reactions using a 9:1 (w/w) mixture of cyclohexanol and [1-^{14}C]cyclohexanone. Previous work has shown that using a comparable mixture of substrates does not have a significant effect on the product distribution.[7] The use of pure ketone as substrate was avoided since we have found that, after an induction period, it can react with uncontrollable violence.

The dicarboxylic acids, from the oxidation of the alcohol/ketone mixtures, were converted into their methyl esters, separated by GC and oxidatively pyrolysed over copper(I) oxide to carbon dioxide. This was trapped and the ^{14}C content was analysed by a scintillation technique. The GC-pyrolysis method was calibrated using multiple injections of solutions of [1-^{14}C]cyclohexanone and was shown to be reproducible to ±3.5%. The percentage retention of ^{14}C in the glutaric and succinic acids was calculated relative to that in the adipic acid and is recorded in Table 5.

The data in Table 5 confirm the results obtained from the methylated cyclohexanols, that glutaric acid is predominantly or exclusively formed by loss of C-2 from the substrate and that succinic acid arises largely from loss of C-2 and C-3. The retention of C-1 in the products is inconsistent with mechanisms involving initial 2-nitrosation followed by further reaction at the 6-position (Schemes 2 and 5).

A number of alternative routes to glutaric and succinic acid involving retention of C-1 of cyclohexanol can be proposed. The starting points for these are the intermediates in Scheme 1. Mechanisms involving the symmetrical species cyclohexane-1,2-dione and intermediates further along the reaction profile should lead to equivalent losses of C-1 and C-2. These may be minor pathways but are not considered further. The mono-oxime of the dione, however, might lead to selective loss of C-2. This possibility was examined further by oxidising 4-methyl-2-hydroxyiminocyclohexanone which showed that, under all the reaction conditions, this substrate gave more 3-methylglutaric acid than the 2-methyl isomer and, in the absence of vanadium(v), more methylsuccinic than succinic acid (Table 2). These results suggest that the ketonic carbon (C-1) rather than the oxime carbon (C-2) is preferentially lost in oxidations of the mono-oxime of cyclohexane-1,2-dione. Furthermore, since the yield of the glutaric acid product from the oxidation of each of the mono-oximes in the absence of catalysts was very low, and much less than that from the equivalent oxidation of cyclohexanol, this cannot be a major pathway in the latter reaction.

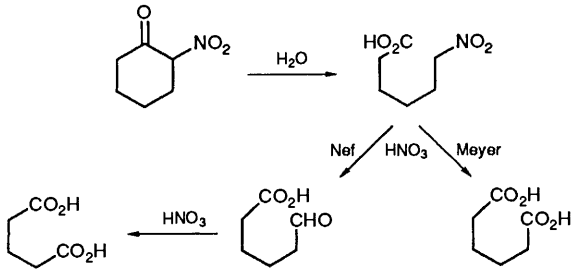
Table 6 Yields of products from reaction of 6-nitrohexanoic acid with nitric acid in the presence of copper(II) and vanadium(V) ions[a]

	Yield of product (%)				
Reaction time/h	Succinic	Glutaric	Adipic	5-Cyanopentanoic	Total
1	—	0.3	10.9	20.8	32.0
96	0.5	3.0	84.2	3.1	90.8

[a] Conditions: see Table 1.

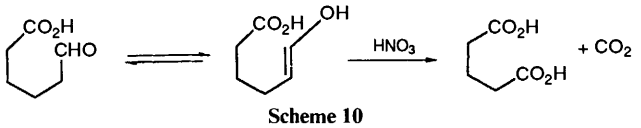
Two other postulated intermediates in the oxidation of cyclohexanol by nitric acid namely, 2-nitro-2-nitrosocyclohexanone and 6-nitro-6-hydroxyiminohexanoic acid, were also prepared and subjected to the reaction conditions (Table 3). Since both these compounds were almost quantitatively converted into adipic acid and neither gave appreciable yields of glutaric or succinic acid, the production of the lower dicarboxylic acids must occur at an earlier point in the reaction. This suggests that either 2-nitroso- or 2-nitro-cyclohexanone may be involved.

2-Nitrocyclohexanone can be hydrolysed to 6-nitrohexanoic acid[8] and this, *via* the Nef reaction[9] in competition with the Meyer reaction,[9b,c,10] provides potential routes to glutaric and adipic acid, respectively (Scheme 9). We examined the oxidation



Scheme 9

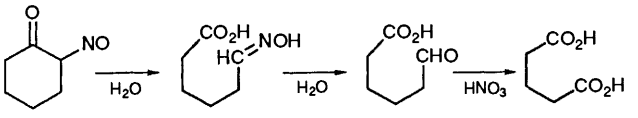
of 6-oxohexanoic acid and, as expected from the analogous reaction of 6-oxoheptanoic acid, this gave largely glutaric acid (Table 3) indicating that oxidation of the enol with carbon loss occurs in preference to the conversion of aldehyde to carboxylic acid (Scheme 10). However, this route to glutaric and succinic



Scheme 10

acid can be rejected since the conversion of 6-nitrohexanoic to 6-oxohexanoic acid is too slow to be part of the nitric acid oxidation of cyclohexanol. After 1 h only 32% reaction had occurred and furthermore the major product was 5-cyanopentanoic acid (Table 6). The reaction of cyclohexanol was typically complete within 0.5 h. When the reaction of 6-nitrohexanoic acid was monitored over 4 d the yield of 5-cyanopentanoic acid was found to build up to a maximum and then decline as adipic acid increased. It is interesting to note, however, that in the industrial oxidation of cyclohexanol/cyclohexanone mixtures 5-cyanopentanoic acid is a trace by-product (<0.05%)[11] and it is possible that this arises by a minor pathway *via* 6-nitrohexanoic acid.

2-Nitrosocyclohexanone provides a further possible route to glutaric and succinic acid. Rogic *et al.*,[12] who have studied the nitrosation of organic compounds, have suggested that 2-nitrosocyclohexanone may be ring-opened by nucleophilic attack on the carbonyl group to yield the oxime of 6-oxohexanoic acid. This would then be expected to give glutaric acid as shown in Scheme 11. Although 2-nitrosocyclohexanone could only be



Scheme 11

prepared as a dimer, it would be expected that in a reaction mixture, it would be formed as a monomer and react as such before it has time to dimerise. For this reason the product distribution obtained from the oxidation of the dimer, which we reported previously,[4] may not reflect the reaction of the monomer. However, the dimer is oxidised to adipic acid and the two lower dicarboxylic acids. Furthermore, oxidation of 6-hydroxyiminohexanoic acid and the corresponding oxo-acid (as described above) occurs readily under the reaction conditions giving both glutaric and succinic acids (Table 3).

We conclude that the predominant pathway to the lower dicarboxylic acid by-products in the oxidation of cyclohexanol by nitric acid involves nucleophilic ring opening of 2-nitrosocyclohexanone leading to the oxidative loss of C-2 (and C-3). The role of the copper(II) catalyst is to favour the reactions of 2-nitrosocyclohexanone which lead to the formation of adipic acid over the nucleophilic ring opening. Loss of C-1 (and C-2 or C-6) can occur *via* a minor pathway to the lower dicarboxylic acid by-products involving oxidation of cyclohexane-1,2-dione which is formed from 2-nitrosocyclohexanone by tautomerisation to the oxime and subsequent hydrolysis. The role of the vanadium(V) ions is to limit the formation of the minor dicarboxylic acids by directing the oxidation of cyclohexane-1,2-dione to give adipic acid.

Experimental

Chromatography and Spectroscopy.—The standard gas chromatographic method used to analyse the dicarboxylic acid oxidation products as their methyl esters has been reported.[4] The spectroscopic methods (MS, IR, ^{1}H and ^{13}C NMR) have also been described.[4]

Materials.—Unless otherwise stated the reagents were commercially available or their preparation was reported in our previous paper.[4]

2,2-Dimethylcyclohexanone was prepared by methylation of 2-methylcyclohexanone followed by separation of the required product from the other compounds by conversion into 2-hydroxymethyl-6,6-dimethylcyclohexanone by the method of King *et al.*[13] Steam distillation in the presence of alkali[13] gave 2,2-dimethylcyclohexanone as a clear oil, b.p. 62–64 °C at 14 mmHg (lit.,[14] 168–174 °C at 740 mmHg). 2,2-Dimethylcyclohexanol was prepared from the ketone by reduction with sodium borohydride to give a clear oil b.p. 71–73 °C at 12 mmHg (lit.,[15] 78–80 °C at 18 mmHg); δ_H 3.30 (1 H, m), 2.72 (1 H, s), 1.90–1.15 (8 H, m), 1.01 (3 H, s) and 0.92 (3 H, s);

δ_C(coupling in off-resonance) 77.0 (d), 38.3 (t), 35.2 (s), 30.4 (t), 28.4 (q), 24.3 (t), 21.4 (t) and 19.2 (q).

6-Oxoheptanoic acid was prepared from 2-methylcyclohexanol, following Schaeffer and Snoddy,[16] as a white crystalline solid m.p. 30–35 °C (lit.,[16] 34–35 °C); δ_H 10.44 (1 H, s), 2.65–2.20 (4 H, m); 2.11 (3 H, s) and 1.87–1.45 (4 H, m); δ_C(coupling in off-resonance) 209.3 (s), 179.0 (s), 43.2 (t), 33.8 (t), 29.8 (q), 24.1 (t) and 23.1 (t).

6-Oxohexanoic acid was prepared by oxidation of 2-hydroxycyclohexanone by the method of Baer[17] and had b.p. 88 °C at 0.1 mmHg (lit.,[17] 144 °C at 8 mmHg); δ_H 9.61 (1 H, t), 9.36 (1 H, s), 2.70–2.15 (4 H, m) and 2.00–1.45 (4 H, m); δ_C(coupling in off-resonance) 202.5 (d), 179.4 (s), 43.4 (t), 33.8 (t), 24.1 (t) and 21.4 (t).

6-Hydroxyiminohexanoic acid was prepared from 6-oxohexanoic acid, with hydroxylamine hydrochloride, as white crystals m.p. 107–113 °C; δ_H(CD_3OD) 7.4 (0.5 H, t, *syn*-isomer) 6.7 (0.5 H, t, *anti*-isomer), 5.3 (2 H, br s), 2.6–2.0 (4 H, m) and 1.9–1.4 (4 H, m); δ_C(CD_3OD)(couplings in off-resonance) 177.3 (s), 152.6 (d, *syn*), 152.1 (d, *anti*), 34.4 (t, *syn* and *anti*), 29.9 (t, *anti*), 27.1 (t, *syn*), 26.5 (t, *syn*); 25.7 (t, *anti*) and 25.3 (t, *syn* and *anti*).

6-Nitrohexanoic acid was prepared from 2-nitrocyclohexanone by the procedure of Matlock and Breslow[18] as a colourless crystalline solid m.p. 21–22 °C (lit.,[18] 21–22 °C); δ_H 8.23 (1 H, s), 4.43 (2 H, t) and 2.60–1.26 (8 H, m); δ_C(coupling in off-resonance) 179.9 (s), 75.4 (t), 33.6 (t), 27.0 (t), 25.6 (t) and 23.8 (t).

4-Methyl-2-hydroxyiminocyclohexanone was prepared from 2-ethoxycarbonyl-4-methylcyclohexanone which had been synthesised from 4-methylcyclohexanone following the method of Ruest *et al.*[19] The ethoxycarbonylcyclohexanone (10 g) was added, under nitrogen, to aqueous potassium hydroxide (4 g in 40 cm^3) over 15 min. This was followed by the slow addition of aqueous sodium nitrite (4.2 g in 20 cm^3). The mixture was stirred for 24 h, cooled to 5 °C and acidified with 6 mol dm^{-3} sulfuric acid (22 cm^3). The 4-methyl-2-hydroxyiminocyclohexanone precipitated from the solution and was recovered by filtration and dried under vacuum to give a white crystalline solid (4.85 g, 68%), m.p. 114–118 °C (lit.,[20] 118 °C); δ_H 10.20 (1 H, br s), 3.50–1.30 (7 H, m) and 1.05 (3 H, d); δ_C(coupling in off-resonance) 196.6 (s), 153.2 (s), 39.6 (t), 33.2 (t), 30.3 (t), 28.4 (d) and 21.5 (q) (Found: C, 59.5; H, 7.9; N, 9.8. Calc. for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92%).

[1-^{14}C]Cyclohexanone was prepared from 1,5-dibromopentane (4.6 g) which was treated with potassium cyanide (1.3 g) containing ^{14}C-labelled potassium cyanide (Amersham; 4.8 mCi) in aqueous ethanol (40:60, 10 cm^3). The mixture was heated under reflux for 2.5 h, cooled and then refluxed again following the addition of unlabelled potassium cyanide (1.43 g). After 2.5 h, the solution was cooled, potassium hydroxide (3 g) in water (6 cm^3) was cautiously added and heating under reflux resumed for a further 3.5 h. Neutralisation with hydrochloric acid and continuous extraction with diethyl ether (6 h) gave, after solvent removal and recrystallisation from toluene, labelled pimelic acid (2.88 g, 87%) with m.p. 100–102 °C (lit.,[21] 98–101 °C). The specific activity, determined by scintillation counting, was 1.447 mCi g^{-1}, giving a radiochemical utilisation of 84%.

The labelled pimelic acid (2.78 g) was converted to [1-^{14}C]cyclohexanone by pyrolysis with barium carbonate (0.2 g) in a pyrex tube at 330–335 °C for 8 h.[22] The cyclohexanone which distilled out was collected in a trap cooled in ice. The contents of the trap were dissolved in diethyl ether, washed with dilute sodium hydroxide solution and dried ($MgSO_4$). Solvent removal gave [1-^{14}C]cyclohexanone (0.75 g, 44%), specific activity 1.176 mCi g^{-1}. GC analysis and ^{13}C and ^{1}H NMR spectroscopy showed the material to be >99% pure.

Oxidation Procedure.—The oxidation procedure and method used for product analysis have been described.[4]

Determination of ^{14}C Content of Dicarboxylic Acid Products.—The crude reaction products from oxidising [1-^{14}C]cyclohexanone were combined with excess of methanol (125 cm^3) and heated to reflux for 5–6 h before being cooled and neutralised with 2 mol dm^{-3} sodium hydroxide. The solvent was removed under reduced pressure and the methyl esters were extracted into diethyl ether, dried ($MgSO_4$) and concentrated. Analysis was by GC using an outlet splitter (25:1). The minor fraction passed into the FID and the major part into a silica tube packed with copper(I) oxide pellets in a Gallenkamp Calbolite Minitube Furnace (Type FS 210) set at 700 °C. The flow of the carrier gas (N_2) through the tube in the furnace was set at 25 cm^3 min^{-1}. The CO_2 from the oxidative pyrolysis of each dicarboxylic acid dimethyl ester eluting from the chromatograph into the furnace was trapped in 10 cm^3 of a scintillation solution [1-phenylethylamine (170 cm^3), 2-(4″-biphenylyl)-5-(4′-*tert*-butylphenyl)-1,3,4-oxadiazole (butyl-PBD) (3.6 g) in methanol (110 cm^3), distilled water (25 cm^3) and toluene (200 cm^3)]. The ^{14}C content of the trapped CO_2 was determined with a Hewlett Packard Tricarb 300C scintillation counter.

Determination of CO_2 Formed during the Oxidation of 6-Oxoheptanoic Acid.—The CO_2 from the oxidation of 6-oxoheptanoic acid was displaced with nitrogen and trapped in a series of microbubblers each containing 15% aqueous sodium hydroxide (5 cm^3). At the end of the reaction, the solutions from the microbubblers were combined and made up to 100 cm^3 with distilled water. The CO_2 content of this solution was determined by passing aliquots (25 mm^3), in a stream of nitrogen and hydrogen, through a tube packed with phosphoric acid on silica at 150 °C followed by a reductor, consisting of a glass tube filled with nickel on firebrick (30–60 mesh) heated to 350–360 °C, connected to a flame ionisation detector. The analysis was quantified with standard solutions of sodium carbonate.

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