Oxidation of α-Substituted Cyclohexanols by Nitric Acid

John R. Lindsay Smith, C. Barry Thomas* and Mark Whittaker
Department of Chemistry, University of York, York YO1 5DD, UK

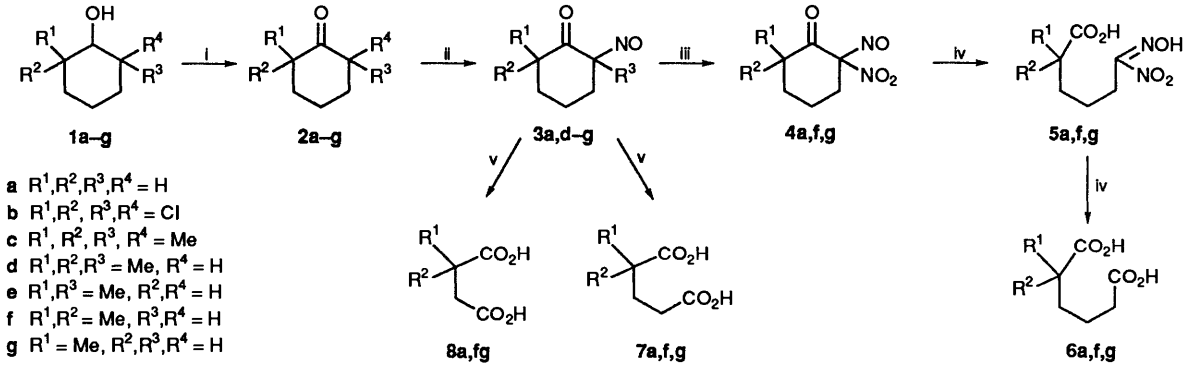
The influence of α-substituents on the oxidative cleavage of cyclohexanol by nitric acid in the presence of copper(II) and vanadium(V) ions has been investigated. Following the initial oxidation to give the cyclohexanone, further reaction, leading to ring opening of the ketone, requires at least one α-hydrogen. Thus 2,2,6,6-tetramethylcyclohexanol is converted to the corresponding ketone whilst 2,2,6-trimethylcyclohexanol is oxidised to a mixture of dicarboxylic acids. The mechanisms of the oxidations are discussed and enolisation is shown to be the key to oxidative cleavage. For ketones that can give two alternative enols, reaction occurs predominantly *via* the more stable tautomer.

A key step in the manufacture of nylon-6,6 is 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 to give adipic acid.[1] The generally accepted view is that the principal reaction pathway involves the sequence, oxidation of cyclohexanol (**1a**) to cyclohexanone (**2a**), nitrosation of (**2a**), to give 2-nitrosocyclohexanone (**3a**), conversion of (**3a**) to 2-nitroso-2-nitrocyclohexanone (**4a**), ring cleavage of (**4a**) to give 6-hydroxyimino-6-nitrohexanoic acid (**5a**), and, finally, hydrolysis of (**5a**) to adipic acid (**6a**) (Scheme 1).[2] We have studied the role of the metal ions in limiting the formation of glutaric acid and succinic acid by-products and have found that there are two pathways to these lower dicarboxylic acids.[3,4] Copper(II) ions favour reactions of 2-nitrosocyclohexanone (**3a**) that lead to formation of adipic acid (**6a**)[4] whilst vanadium(V) ions enhance the yield of adipic acid from the oxidation of cyclohexane-1,2-dione, which is formed from 2-nitrosocyclohexanone (**3a**) by tautomerisation to the oxime and subsequent hydrolysis.[3] During the course of these investigations we also studied the effect of α-substituents on the product distribution from cyclohexanols. We report here on these results and the light they throw on the oxidation of alcohols, and in particular, cyclohexanol, by nitric acid.

Results and Discussion

α-Substituted cyclohexanols (**1b–g**) were oxidised by nitric acid in the presence of catalytic amounts of vanadium(V) and copper(II) ions using the method we have described previously.[3] No reaction was observed for 2,2,6,6-tetrachlorocyclohexanol (**1b**), the oxidation of 2,2,6,6-tetramethylcyclohexanol (**1c**) gave the corresponding ketone (**2c**), and dicarboxylic acid products were formed from the oxidation of the trimethylated, dimethylated and monomethylated cyclohexanols (**1d–g**) (Table 1). All the dicarboxylic acids (**6a**, **f**, **g**; **7a**, **f**, **g** and **8a**, **f**, **g**) formed in the oxidations were stable under the reaction conditions.

The first step in the oxidation of cyclohexanol is considered to be formation of cyclohexanone and nitrous acid which is followed by reaction of a nitrosonium ion, generated from this acid, with the enol tautomer of the ketone.[2] Sojka *et al.*, however, claim that cyclohexanone is not an intermediate, since the oxidation of cyclohexanol is more rapid than that of cyclohexanone.[5] We argue that the oxidation of **1c** to give **2c** in this study suggests that cyclohexanone is indeed formed in the oxidation of cyclohexanol and that further reaction involves enolisation. This latter step cannot occur for a tetra-α-substituted ketone such as **2c**. The slower oxidation of cyclohexanone, reported by Sojka *et al.*, presumably results from a requirement for nitrous acid to effect α-nitrosation of the enol. When cyclohexanol is the starting material, nitrous acid is formed in the conversion of the alcohol to the ketone, whereas with cyclohexanone as substrate this step in the overall reaction is absent and the initial concentration of nitrous acid will be very low. In agreement with this mechanistic interpretation, we have observed that the oxidation of pure cyclohexanone by nitric acid shows an induction period, presumably while the nitrous acid concentration builds up, and can then proceed with uncontrollable violence.[4] However, no oxidation was observed when 2,2,6,6-tetrachlorocyclohexanol (**1b**) was used as the substrate. The lack of reactivity of substrate **1b** is presumably due to an electronic rather than a steric effect since a chloro-substituent should be of similar size to a methyl group. Whilst the mechanism by which nitric acid oxidises alcohols to ketones has not been established, it has been suggested that reaction is mediated by nitrosonium ions, either by hydride ion abstraction[6] followed by attack of water[7] or alternatively by a radical cation process.[8] Both mechanisms involve the

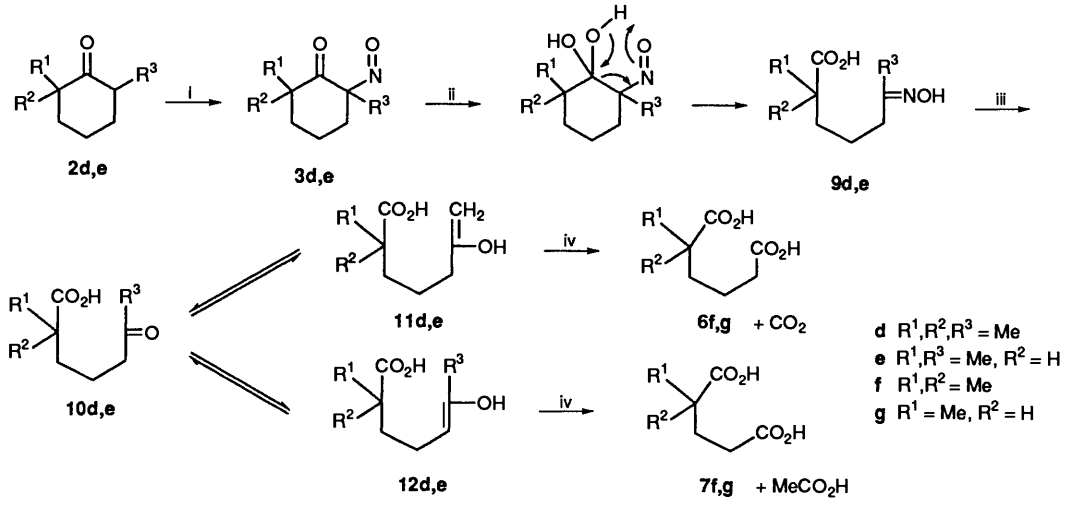


Scheme 1 *Reagents:* i, HNO_3, $-HNO_2$; ii, HNO_2; iii, HNO_3; iv, H_3O^+; v, multiple steps

Table 1 Product yields from the oxidation of cyclohexanol, α-substituted cyclohexanols and 2-methyl-6-oxoheptanoic acid by nitric acid[a]

Substrate	Yield (%) Cyclohexanone	Adipic	Glutaric	Succinic	Acetic	CO_2	Total yield of dibasic acids (%)
1a	0	94.6 (**6a**)	3.7 (**7a**)	1.7 (**8a**)	—	—	100.0
1b	0	0	0	0	—	—	0 (93)[b]
1c	93 (**2c**)	0	0	0	—	—	93 (94)[c]
1d	0	25.6 (**6f**)	65.5 (**7f**)	1.8 (**8f**)	—	—	92.9
1e	0	20.9 (**6g**)	70.5 (**7g**)	0.9 (**8g**)	65.7	19.5	92.3
1f	0	84.5 (**6f**)	8.0 (**7f**)	4.0 (**8f**)	—	—	96.5
1g	0	15.8 (**6a**)	58.9 (**7a**)	4.7 (**8a**)	57.9	19.5	99.5
		20.1 (**6g**)	⩽0.5 (**7g**)	⩽0.5 (**8g**)			
10e	—	21.9 (**6g**)	77.1 (**7g**)	⩽0.2 (**8g**)	—	—	99.0

[a] Conditions: temperature 73 °C, 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.[3] [b] Recovered alcohol **1b**. [c] Including 1% recovered alcohol **1c**.



Scheme 2 *Reagents:* i, HNO_2; ii, H_2O; iii, H_3O^+; iv, multiple steps

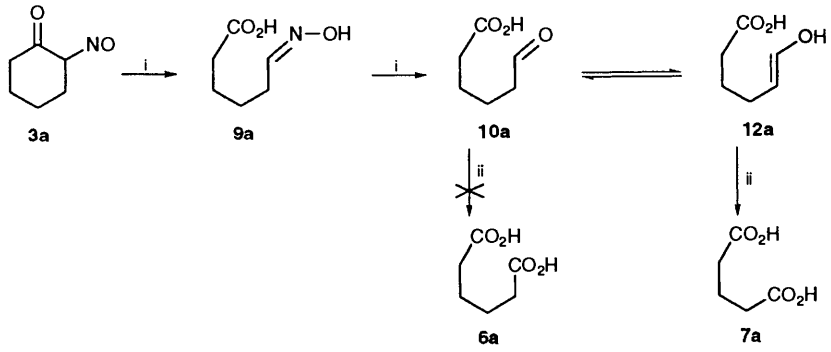
development of a degree of electron deficiency on C-1, a process that would be inhibited by the strong electron-withdrawing inductive effect of the chlorine substituents.

Evidence for enolisation of cyclohexanone being a key-step in the reactions leading to dicarboxylic acids is that oxidation proceeds beyond the initial ketone stage if at least one α-position is unsubstitued, as is found for the methylated cyclohexanols (**1d–g**). Not surprisingly the presence of the methyl groups can alter the product distribution relative to that from cyclohexanol (Table 1).[3] For each of the substrates **1a** and **1d–g**, the enol tautomer of the ketone is able to undergo nitrosation and in all instances the resultant nitrosoketone reacts further. In the case of 2,2-dimethylcyclohexanol (**1f**) the course of reaction is virtually identical to that of cyclohexanol itself, the dimethylated dibasic acids being formed in similar yields to the dibasic acids from cyclohexanol.

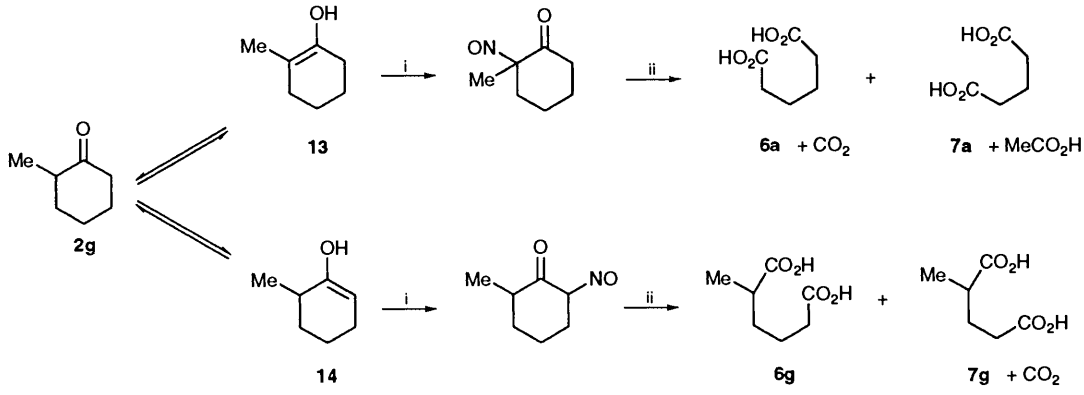
Interestingly, the reactions of 2,2,6-trimethyl- and 2,6-dimethyl-cyclohexanol (**1d** and **e**) show that oxidation is not blocked at the stage following the formation of the 2-nitrosocyclohexanone derivatives **3d** and **e**, respectively. Thus, although **3d** is unable to form the 2-nitro-2-nitroso derivative equivalent to **4** without the cleavage of a methyl group, oxidation proceeds to give a good yield of dicarboxylic acids. We presume that further reaction occurs *via* ring opening, possibly through hydration of the nitrosoketone (**3d**) followed by an electrocyclic ring cleavage,[9] to give 2,2-dimethyl-6-hydroxyiminoheptanoic acid (**9d**).[10] This, under acidic conditions, is likely to hydrolise to 2,2-dimethyl-6-oxoheptanoic acid (**10d**) (Scheme 2).The ketone **10d** can form two enols **11d** and **12d** oxidation of which would give, respectively, 2,2-dimethyladipic acid (**6f**) and 2,2-dimethylglutaric acid (**7f**). Similar arguments apply to the oxidation of 2,6-dimethylcyclohexanol (**1e**).

Thus, the dibasic acid product distribution from substrates **1d** and **e** should be governed by either the equilibrium concentrations of the alternative enol tautomers of the 6-oxoheptanoic acids or their relative rates of formation and reactivities. The results show that the enols with the internal double bond, **12d** and **e**, which would be expected to be more stable than the isomers with the double bond in a terminal position, **11d** and **e**, lead to the major dicarboxylic acid products, **7f** and **g**. This is consistent with the product distribution being controlled by the equilibrium concentration of enols **11** and **12** rather than their relative reactivities. In support of this view, we found that oxidising 2-methyl-6-oxoheptanoic (**10e**), the putative intermediate in the oxidation of **1e**, gives 2-methylglutaric acid (**7g**) as the major product. The slight discrepancy in product distributions from **1e** and **10e** could stem either from a limited amount of oxidation of the hydroxyimino acid (**9e**) competing with its hydrolysis or from differences in the amounts, and relative proportions of nitrogeneous oxidants in the system when oxidising the ketone **10e** directly rather than as an intermediate formed through initial oxidation of the cyclohexanol **1e**.

That the mechanism proposed above for cyclohexanols **1d** and **e** is not a major pathway in the oxidation of cyclohexanol to adipic acid was confirmed by us in an earlier study.[4] Thus, the ring opening of 2-nitrosocyclohexane (**3a**), equivalent to the conversion of **3e** to **9e**, would, after hydrolysis, lead to the formation of 6-oxohexanoic acid (**10a**). However, oxidation of



Scheme 3 *Reagents:* i, H_2O; ii, HNO_3



Scheme 4 *Reagents:* i, HNO_2; ii, multiple steps

this gives glutaric acid (**7a**), as predicted by the mechanism in Scheme 2, rather than adipic acid (**6a**) arising from oxidation of the aldehyde group (Scheme 3).

There remains the oxidation of 2-methylcyclohexanol (**1g**), where competitive oxidative cleavage of the C-1–C-2 bond (*cf.* reactions of **2d** and **e**, Scheme 2) and of the C-1–C-6 bond (*cf.* reactions of **2a** and **f**, Scheme 1) can occur. This has been studied previously by Sojka *et al.* who reported the major products to be 2-methylglutaric acid (**7g**) and 2-methyladipic acid (**6g**) from C-1–C-6 cleavage.[5] In contrast, we found in this study that glutaric acid (**7a**) (together with an equivalent quantity of acetic acid) rather than 2-methylglutaric acid (**7g**) predominates. Again our product distribution is consistent with reaction of the more highly substituted, and presumably more stable, enol tautomer of 2-methylcyclohexanone **13** in preference to **14**, leading to cleavage of the C-1–C-2 bond rather than the C-1–C-6 bond (Scheme 4).

The results above demonstrate that substitution in the α-position of cyclohexanol has a significant effect upon the course of oxidation by nitric acid. Furthermore, they are consistent with enolisation of cyclohexanone being a key step in the production of adipic acid from cyclohexanol.

Experimental

Methods.—The oxidation procedure, the GC methods used to analyse the oxidation products and the spectroscopic methods (MS, IR, ^1H and ^{13}C NMR) have been described previously.[3]

Materials.—Unless stated below the reagents were commercial materials or their preparation was reported in our earlier papers.[3,4]

2,2,6,6-*Tetramethylcyclohexanol* was prepared from 2-methylcyclohexanone. The latter ketone (20 g) was added dropwise to a stirred slurry of sodium hydride (80% powdered dispersion in oil, 10 g) in 1,2-dimethoxyethane (100 cm^3), the mixture refluxed for 16 h and allowed to cool. Iodomethane (30 g) was added dropwise and the mixture heated at reflux for 24 h and cooled. Methylation was repeated twice more using an identical procedure. Finally the mixture was cooled, distilled water (100 cm^3) added cautiously and the mixture acidified with hydrochloric acid. The organic layer was separated and the aqueous layer extracted with diethyl ether. The combined organic material was washed with sodium thiosulfate solution and distilled water, dried ($MgSO_4$) and the solvent removed to give a light yellow oil which was purified by chromatography on a 60–120 mesh silica gel column using a graded mixture of light petroleum (b.p. 40–60 °C)–propanone as the eluent to give 2,2,6,6-tetramethylcyclohexanone (10 g, 36%) as a colourless oil contaminated with a small amount (*ca.* 2%) of 1-methoxy-2,2,6,6-tetramethylcyclohexane.[11]

The product was dissolved in methanol (75 cm^3) cooled in an ice–salt mixture and sodium borohydride (3 g) dissolved in ice-cold slightly alkaline distilled water (75 cm^3) was added slowly with stirring over 2 h. Cautious acidification with hydrochloric acid (2 mol dm^{-3}), extraction with diethyl ether followed by washing of the organic extracts with aq. sodium hydrogen carbonate, drying ($MgSO_4$), solvent removal and distillation gave 2,2,6,6-tetramethylcyclohexanol (3.7 g, 36%) as a colourless oil, b.p. 76 °C/18 mmHg (lit.,[12] 72–74 °C/12 mmHg); δ_H 3.00 (1 H, s, D_2O exch.), 1.70 (1 H, s), 1.50–1.25 (6 H, m), 1.00 (6 H, s) and 0.91 (6 H, s); δ_C(coupling in off-resonance) 84.2 (d), 40.1 (t), 35.9 (s), 31.9 (q), 19.8 (q) and 18.6 (t).

2,2,6-*Trimethylcyclohexanol* was prepared from 2-methylcyclohexanone by ethoxycarbonylation of the ketone using the method of Reust *et al.*[13] to give a mixture of 2-ethoxycarbonyl-2-methylcyclohexanone and 2-ethoxycarbonyl-6-methylcyclohexanone as a colourless oil (b.p., 60–65 °C/0.05 mmHg). This mixture (34 g) was methylated by the method of Stevens and Weinheimer[14] to give 2-ethoxycarbonyl-2,6,6-trimethylcyclohexanone (23.0 g, 59%) as a colourless oil, b.p. 92–96 °C/1.5 mmHg (lit.,[14] 118–126 °C/15 mmHg). The ketoester (22.9 g)

was converted to 2,2,6-trimethylcyclohexanone (10.9 g, 72%)[14] and this ketone reduced with sodium borohydride as in the preparation of 2,2,6,6-tetramethylcyclohexanol to give a mixture of stereoisomers of 2,2,6-trimethylcyclohexanol (3.9 g, 35%) as a colourless oil, b.p. 82 °C/18 mmHg (lit.,[15] 75–78 °C/14 mmHg); δ_H 3.13 (0.3 H, m), 2.83 (1 H, d), 2.49 (1 H, s, D_2O exch.), 2.03 (0.7 H, m), 1.95–1.15 (6 H, m), 1.02 (3 H, s), 0.98 (3 H, d) and 0.92 (3 H, s).

2,2-Dimethyladipic acid was obtained by oxidising 2,2-dimethylcyclohexanol (3 g) with nitric acid (55%, 20 cm^3) using a scaled up version of the analytical procedure. After completion of the oxidation, the reaction mixture was cooled to 0 °C, the resultant precipitate filtered off and recrystallised, firstly from aq. ethanol and then from a trichloromethane–tetrachloromethane mixed solvent to give 2,2-dimethyladipic acid (1.1 g, 27%) as white crystals, m.p. 87–89 °C (lit.,[16] 86–88 °C); δ_H 11.86 (2 H, s, D_2O exch.), 2.35 (2 H, m), 1.80–1.45 (4 H, m) and 1.25 (6 H, s); δ_C(coupling in off-resonance) 184.8 (s), 180.1 (s), 42.0 (s), 39.5 (t), 34.3 (t), 24.8 (q) and 20.2 (t).

2-Methyladipic acid was obtained from 2-ethoxycarbonylcyclopentanone (19 g) which was added dropwise to finely divided sodium (2.85 g) in benzene (100 cm^3) under nitrogen. The mixture was heated to 60 °C and stirred for 24 h. After cooling iodomethane (21 g) was added dropwise and the mixture left for 5 h before being heated at 60 °C for a further 24 h. The solution was cooled to 0 °C before ethanol (5 cm^3) followed by distilled water (20 cm^3) was added cautiously and the mixture was extracted with diethyl ether. The extracts were washed with sodium thiosulfate solution, dried ($MgSO_4$), concentrated and distilled to give 2-ethoxycarbonyl-2-methylcyclopentanone (14.5 g, 70%) as a colourless oil, b.p. 64–65 °C/0.15 mmHg (lit.,[17] 117–121 °C/15 mmHg). A mixture of the keto-ester (14 g), sodium (0.3 g) and ethanol (20 cm^3) was allowed to stand for 2 h at room temp., the solvent removed and the residue treated with sulfuric acid (1 mol dm^{-3}, 50 cm^3) at 95 °C for 24 h. After basification the solution was washed with diethyl ether, acidified, extracted with diethyl ether, the extracts dried ($MgSO_4$) and the solvent removed. The residue was recrystallised from a tetrachloromethane–ethanol mixture after treatment with decolourising charcoal to give 2-methyladipic acid (4.1 g, 31%) as white crystals, m.p. 55–58 °C (lit.,[18] 63–64 °C); δ_H 11.50 (2 H, s, D_2O exch.), 2.70–2.05 (3 H, m), 1.95–1.40 (4 H, m) and 1.17 (3 H, d); δ_C(coupling in off-resonance) 183.2 (s), 180.1 (s), 39.2 (d), 33.9 (t), 32.7 (t), 22.2 (t) and 16.8 (q).

2-Methyl-6-oxoheptanoic acid was prepared from 2,6-dimethylcyclohexanol by a modification of the method used by Schaefer and Snoddy[19] for the synthesis of 6-oxoheptanoic acid and was obtained in 31% yield as a colourless oil, b.p. 100–102 °C/0.1 mmHg (lit.,[20] 155–156 °C/7 mmHg), δ_H 9.48 (1 H, s, D_2O exch.), 2.72–2.22 (2 H + 1 H, m), 2.17 (3 H, s), 1.88–1.37 (4 H, m) and 1.20 (3 H, d); δ_C 209.3 (s), 182.4 (s), 43.4 (t), 39.2 (d), 32.8 (t), 29.9 (q), 21.3 (t) and 16.8 (q).

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