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Oxidation of 2-Methylcyclohexanone and Cyclohexanone by Dioxygen Catalyzed by Vanadium-Containing Heteropolyanions

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2-Methylcyclohexanone is oxidized by dioxygen in the presence of $H_{3+n}[PMo_{12-n}V_nO_{40}]\cdot aq$ to give 6-oxoheptanoic acid. Solvent effects are studied. The same precursors with cyclohexanone in aqueous acetic acid give adipic acid as the major product and other dicarboxylic acids by oxidation of 6-oxohexanoic acid.

Oxidations of organic compounds by dioxygen have been reported for a number of homogeneous transition-metal catalysts;[1,2] those by quinquevalent vanadium have, besides their own interest, implications concerning the behavior of vanadium oxide catalysts. The subject was first examined by Morette *et al.* essentially from an analytical viewpoint[3] and later by Littler *et al.*;[4] dioxygen has no significant effect on the rates of oxidation, and all these oxidation processes are stoichiometric. The catalyzed oxidation of cyclohexane,[5-8] of cyclohexanone,[9-18] or of cyclohexanol/cyclohexanone mixtures[19] to yield predominantly adipic acid (1,6-hexanedioic acid) has been the subject of considerable study. This diacid is the most important of all the aliphatic α,ω-dicarboxylic acids.[20] Adipic acid is produced by nitric acid oxidation of cyclohexanol[19,21] or cyclohexanol/cyclohexanone mixtures.[20] Typical reaction conditions involve 50-60% nitric acid containing a copper(II)-vanadium(V) catalyst at 60-80 °C. A number of alternatives to nitric acid oxidation have been investigated. The one-pot cobalt(III)-catalyzed O_2 oxidation of cyclohexane to adipic acid is a subject of continuing interest.[5-8,22] Maximum adipic acid product selectivity (77%) is attained at 100 °C and at 85% cyclohexane conversion.[22] In recent work, the oxidation of cyclohexanone in AcOH over CeO_2 in the presence of dioxygen was studied at 98-118 °C and 5-15 atm.[23] This reaction gives caprolactone and dicarboxylic acids; carbon oxides are produced in small amounts. We recently described the preparation of keto acids involving O_2 oxidation of α-substituted cycloalkanones in the presence of oxovanadium(IV) or -(V) complexes, heteropolyacid $H_5[PMo_{10}V_2O_{40}]\cdot aq$, or copper complexes as catalyst precursors.[24] Other authors have reported that cyclic aliphatic compounds or ketones are oxidized in the liquid phase under anaerobic conditions by a vanadium-containing heteropolyanion, generally with the Keggin structure $A_m[XY_{12-n}V_n^{5+}O_{40}]$ (A = H, Li, etc.; X = P, Si, etc.; Y = Mo or W; $1 < n < 10$; $m = 3 + n$, $4 + n$, etc.).[15]

Other results concerning homogeneous vanadium-based oxidizing systems with O_2 have been reported.[25-27] Heteropolyacids, $H_{3+n}[PMo_{12-n}V_nO_{40}]\cdot aq$ (denoted HPA-*n*), are privileged precursors for the oxidative cleavage of substituted or nonsubstituted cycloalkanones.[24a,b] In this paper we report a comparative study of the oxidation of 2-methylcyclohexanone and of cyclohexanone to 6-oxoheptanoic acid or 1,6-hexanedioic acid, respectively, by *dioxygen* in the presence of HPA-*n*, which are soluble in an aqueous phase and in organic solvents such as MeCN, AcOH, etc. These HPA-*n* were prepared by standard methods.[28]

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Table I. Oxidation of 2-Methylcyclohexanone, 1, by HPA-*n* (*n* = 2 or 4)/O_2[a]

entry	precursors	solvent (mL)	time (h)	conversn[b] (%)	yield[c] (%) 2	3	4
1	$H_5[PMo_{10}V_2O_{40}]\cdot 30H_2O$	MeCN (6)	4	98	85	2	9
2	$H_5[PMo_{10}V_2O_{40}]\cdot 30H_2O$	H_2O (2)	24	75	75		
3	$H_7[PMo_8V_4O_{40}]\cdot 12H_2O$	H_2O (2)	8	99	97 (70)[d]		
4	$H_5[PMo_{10}V_2O_{40}]\cdot 30H_2O$	AcOH/H_2O (4.5/0.5)	1	99	90 (75)[d]		3
5[e]	$Q_5[PMo_{10}V_2O_{40}]\cdot$aq	MeCN (6)	24				
6[f]	$V_2O_5/MoO_3/H_3PO_4$	H_2O	24	99	98		

[a] Reaction conditions: HPA-*n* (*n* = 2 or 4) (0.075 mmol), 1 (12.4 mmol), 60 °C, O_2 (1 atm), internal standard: heptanoic acid. [b] % of substrate consumed. [c] Products identified by coupled GC–MS and ^1H and ^{13}C NMR. [d] Isolated material. [e] Q = $(n\text{-Bu})_4N^+$, $C_5H_5N^+(CH_2)_{15}Me$, $Me(CH_2)_5N^+$, etc. [f] V (2 mmol); Mo (5 mmol); H_3PO_4 (1.1 mmol), see Experimental Section.

Table II. Oxidation of Cyclohexanone, 5, with HPA-2/O_2:[a] Solvent Effect

entry	solvent (mL)	temp (°C)	time (h)	conversn[b] (%)	yield[c] (%) 7	8	9
1	MeCN (50)	70	24	85	24	10	3
2	*t*-BuOH (50)	72	24	90	23	17	4
3	EtOH (50)	65	24	84	23[d]	15[d]	2[d]
4	AcOH (50)	72	24	54	6	5	1
5	AcOH/H_2O (47.5/2.5)	70	13	87	23	11	3
6	AcOH/H_2O (45/5)	70	7	99	40	23	4
7	AcOH/H_2O (40/10)	70	15	99	40	15	4
8	AcOH/H_2O (35/15)	70	24	99	38	16	3
9	AcOH/H_2O (25/25)	70	24	98	28	17	3
10	H_2O (50)	68	24	67	18	10	2

[a] Reaction conditions: HPA-2 (2.2 mmol), 5 (482.4 mmol), 70 °C, O_2 (1 atm, 14.5 L·h^{-1}). [b,c] Cf. Table I. [d] Diethyl esters.

Table III. Oxidation of Cyclohexanone, 5, by Vanadium Oxo Complexes or Heteropolyacids and Dioxygen[a]

entry	precursors (mmol)	time(h)	conversn[b] (%)	yield[c] (%) 7	8	9
11	$VO(acac)_2$ (4.32)	16	98	32	12	6
12	$VO(O\text{-}i\text{-}Pr)_3$ (1.3)	10	99	24	14	6
13	$VO(O\text{-}i\text{-}Pr)_3$ (9.4)	10	99	33	13	5
6	$H_5[PMo_{10}V_2O_{40}]\cdot 30H_2O$ (2.2)	7	99	40	23	4
14	$H_7[PMo_8V_4O_{40}]\cdot 12H_2O$ (1.1)	7	99	50	19	3

[a] Reaction conditions: 5 (482.5 mmol), AcOH/H_2O (45 mL/5 mL), 70 °C, O_2 (1 atm, 14.5 L·h^{-1}). [b,c] Cf. Table I.

Treatment of 2-methylcyclohexanone (**1**) (Table I) with HPA-2/O_2 in acetonitrile gives 6-oxoheptanoic acid (**2**), acetic acid (**3**), and cyclopentanone (**4**) (entry 1). A solvent effect on the oxidation of **1** was found. Thus, in water the same reaction gives **2** selectively (entries 2 and 3). In both cases, total conversion of the substrate can be obtained in a reasonable time. In Table I, the results of the comparison of the catalytic activity of heteropolyacids (entries 1 and 3) *vs* their onium salts (entry 5) show that the former are active precursors whereas the latter do not show even the slightest activity. The Brönsted acidity of the HPA-*n* is a key parameter of the catalytic system; it could influence the formation of enolate[29] and the reoxidation of the reduced catalyst. The lack of reaction with the salts of HPA's versus HPA's can also be explained by the known drop in redox potential of vanadium(V) with decreasing Brönsted acidity.[30] The data (entry 6) show that the HPA-*n* species can be formed *in situ* from a $MoO_3/V_2O_5/H_3PO_4/H_2O$ mixture, thus avoiding the tedious preparation with Et_2O extraction.[28a]

Similar solvent effects are found for the cleavage of cyclohexanone (**5**) (Table II). All the reactions can be performed catalytically; usually, the mole ratio of cyclohexanone/HPA-*n* was 220. In all experiments, the oxidation of **5** leads to the formation of adipic acid as the major product, together with glutaric and succinic acids. Carbon oxides are evolved during the reaction; they are produced by subsequent reaction in a homolytic process, but in no case do they arise from the oxidation of adipic acid, since this dicarboxylic acid is inert to degradation by HPA-*n* (*n* = 2 or 4)/O_2 systems, contrary to observations with cobalt precursors.[18]

Moreover, GC–MS coupling experiments indicate the formation of 6-oxohexanoic acid (**6**). With 2-methyl-2-propanol and ethanol, the reaction does not go to completion in 24 h (entries 2 and 3). The AcOH/H_2O (45/5) mixture is one of the most convenient media for controlling these reactions. The presence of water in the reaction mixture moderates the initial regime and improves adipic acid selectivity. The conversion of **5** was 99% in 7 h, yielding (after esterification with methanol) dimethyl adipate (**7**) (40%), dimethyl glutarate (**8**) (23%), and dimethyl succinate (**9**) (4%) (entry 6). The use of either water or pure acetic acid alone gives lower cyclohexanone conversions (entries 4 and 10); the decarboxylation of acetic acid does not occur under these conditions. It should be noted that some solvents cause inhibition ($C_2H_4Cl_2$, AcOMe).

Table III shows that vanadium(IV) acetylacetonate or vanadium(V) oxoalkoxide can also have a catalytic effect with dioxygen (entries 11–13). Furthermore, we observed that the use of HPA-4 instead of HPA-2 increases the reactivity and that the yield of dimethyl adipate reaches 50% (entry 14). This result can be correlated with the high Brönsted acidity of the reagent,[30] since ketones are more reactive in the enol form.[31,32]

Comparative studies of the reactivity of **1** and **5** (Scheme I) suggest that the byproducts (glutaric, succinic acids, and carbon oxides) arise predominantly by 6-oxohexanoic acid degradation. This postulated intermediate and the corresponding ester were prepared[33] and oxidized under the same reaction conditions (Table IV). Both **6** and methyl 6-oxohexanoate yield **7**–**9** upon oxidation (entries 15 and 16). We propose that in the presence of excess

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Scheme I

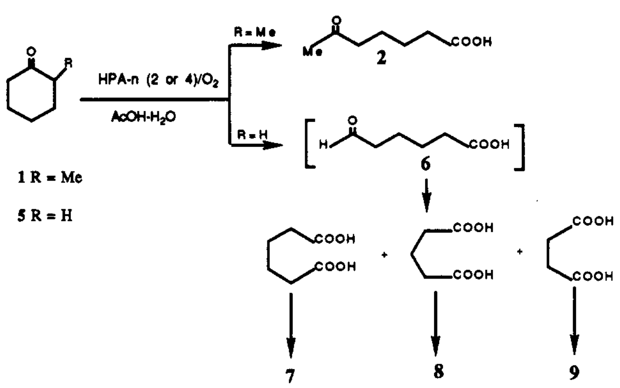

Table IV. Yields of Products from the Oxidation of 6-Oxohexanoic Acid, Methyl 6-Oxohexanoate, and 2-Hydroxycyclohexanone with HPA-2/AcOH–H_2O/O_2 System[a]

entry	substrate	time (h)	conversn[b] (%)	yield[c] (%) 7	8	9
15	$HO_2C(CH_2)_4CHO$	15	99	43	23	4.5
16	$MeO_2C(CH_2)_4CHO$	20	99	40	20	3.5
17	$HOC_6H_9(=O)$	10	99	88	2	0.5

[a] Reaction conditions: substrate (10 mmol), HPA-2 (0.075 mmol), 70 °C, O_2 (1 atm, 14.5 $L \cdot h^{-1}$), AcOH/H_2O (4.5 mL/0.5 mL). [b,c] Cf. Table I.

dioxygen, 6 undergoes oxidative dehydrogenation more easily than aldehyde is converted to dicarboxylic acid. The methyl substituent, which leads to ketone formation in the case of 1, is all-important.[13] The oxidation of 6 (which has been identified as an intermediate) to adipic acid is the major problem to be resolved.

The reaction of 2-hydroxycyclohexanone with the HPA-2/AcOH–H_2O/O_2 system was also examined. We observed a dramatic effect on the product distribution (entry 17). This substrate gives the highest dimethyl adipate yield (88%). These results differ markedly from those obtained in the earlier work with CrO_3[34] or Co(II)[35] which gave 6-oxohexanoic acid as a final product. In our opinon, 2-hydroxycyclohexanone could only be a minor intermediate, and the hydroxylation of cyclohexanone does not seem to be a key step under our conditions.

The present results are the first examples of the catalytic oxidation of 5 to adipic acid with HPA-*n* (*n* = 2 or 4)/ AcOH–H_2O/O_2 systems which are highly efficient under very mild conditions. Using O_2 instead of HNO_3 presents serious advantages: there is no risk of corrosion, and no nitrogen oxides need to be recovered. Further research is directed toward elucidating the oxidation mechanism, and work is in progress to catalyze the transformation of ω-oxocarboxylic acids to dicarboxylic acids, which seems to be the rate-limiting step in this oxidation.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a Fourier transform apparatus (Bruker WP200), using $CDCl_3$ as solvent. The heteropolyacids $H_{3+n}[PMo_{12-n}V_nO_{40}]\cdot aq$ (*n* = 2 or 4) were prepared by standard methods.[28] Unless otherwise stated, the inorganic reagents were commercially available. 2-Methylcyclohexanone (Aldrich), cyclohexanone (Prolabo), and 2-hydroxycyclohexanone (Aldrich) were better than 99% pure by GC analysis; they were used without further purification.

6-Oxohexanoic acid and methyl 6-oxohexanoate were prepared by oxidation of 2-hydroxycyclohexanone[33a] and cyclohexene,[33b] respectively.

The $H_{3+n}[PMo_{12-n}V_nO_{40}]$ species can be prepared by boiling stoichiometric amounts of molybdenum trioxide (45 mmol), vanadium pentoxide (9 mmol), and phosphoric acid (10 mmol) in water (80 mL) *under dioxygen* for 24 h. Aliquot volumes (*e.g.*, 9 mL) are used for a catalytic test with 2-methylcyclohexanone (see Table I). From ^{31}P NMR measurements it was found that the precursors are not pure heteropolyacids: HPA-2 contains, in fact, a certain fraction of HPA-1 and HPA-3, and with HPA-4 several isomers are identified in the solution. We were unable to prepare a 99% pure isomer.

Analysis and Identification of Products. GC/MS Data System. The reaction mixtures were analyzed by GC (Girdel 30 and Girdel 330 FID apparatus). The columns were 3% OV 17 on Chromosorb Q (3 m) and OV 1701 (capillary column: 0.25 mm × 50 m), with N_2 or He as carrier gas. Product yields were determined by using heptanoic acid as internal standard. Detector response factors were calibrated by using stock solutions of authentic samples at concentrations similar to those encountered in the oxidation reactions. The cumulative errors resulting from response factor calibration, base line treatment, purity of standards, etc. are believed to be 5–8% or less in most cases. Mass spectral data were obtained at 70 eV using a Kratos MS 50 spectrometer with a DS 55 data system or a Delsi-Nermag R10-10 coupled with a GC apparatus (Girdel 30).

Oxidation of 1. The typical experiment was performed in an all-glass reactor vessel (40 mL) which was attached to a vacuum line with a manometer and a gas inlet. It was charged with HPA-*n* (*n* = 2 or 4) (*V* = 0.150 mmol) and AcOH/H_2O (5 mL, 9:1), and the mixture was stirred magnetically under O_2 at 20 °C for 5 min. Ketone 1 (12.5 mmol) was syringed in through a suba-seal. The vessel was then immersed in a bath preheated to 60 °C, and the deep brown mixture was vigorously stirred for the time indicated in the tables. Dioxygen uptake was determined by means of a gas burette system. The mixture was cooled and analyzed by GC. After evaporation of AcOH/H_2O, Et_2O (15 mL) was added to the oily residue. The solution thus obtained was extracted with aqueous sodium bicarbonate Na_2CO_3 solution (10%; 2 × 10 mL). The aqueous layer was washed with Et_2O (2 × 10 mL) and then acidified to pH 1 with HCl (10 N). Brine was added to the resultant mixture. The combined aqueous solution was extracted with Et_2O (2 × 15 mL) and the ethereal layer concentrated to afford the keto acid after distillation (bp (°C)/Torr: 160–162/2).

6-Oxoheptanoic acid (2): ^1H NMR δ 1.64 (m, 4H), 2.16 (s, 3H), 2.39 (m, 2H), 2.48 (m, 2H), 10.10 (s, 1H); ^{13}C NMR δ 23.0, 24.05, 29.9, 33.7, 43.15, 179.3, 209.5; MS (70 eV) *m/z* = 144 (M^+).

Oxidation of 5. A double-jacketed reactor (200 mL) was equipped with a thermometer, a reflux condenser, two side arms with a gas inlet and outlet, and a central four-bladed propeller (800–1200 rpm). The oxidizing solution AcOH/H_2O (50 mL; 9:1) with HPA-2 (2.20 mmol) or HPA-4 (1.10 mmol) was introduced and heated to 70 °C with stirring while O_2 was bubbled through at *ca.* 14.5 $L \cdot h^{-1}$; the substrate, 5, was then added (482.5 mmol) and the mixture heated at 70 °C for *ca.* 7 h. After being cooled to 50 °C, an aliquot portion (usually 10 mL) including a standard (heptanoic acid) was esterified under dinitrogen, using a large excess of refluxing methanol (100 mL; 24 h) in the presence of sulfuric acid (98%; 0.3 mL). The yields of the diesters 7–9 were calculated from the GC measurements.

Methyl 6-oxohexanoate: MS (CI, NH_3) *m/z* = 145 (90), 162 (32); MS (70 eV) *m/z* = 116 (33), 113 (59), 112 (30), 74 (60), 54 (90).

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