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Extending the Haloform Reaction to non-Methyl Ketones: Oxidative Cleavage of Cycloalkanones to Dicarboxylic Acids using Sodium Hypochlorite under Phase Transfer Catalysis conditions

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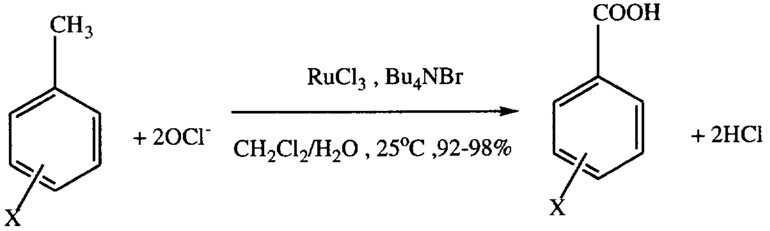
Abstract: Cyclohexanone is readily oxidized to adipic, α,α - dichloroadipic, glutaric and succinic acids by sodium hypochlorite under phase transfer conditions. The selectivity is highly dependent on the pH of the reacting system. A consecutive chlorination-hydrolysis mechanism is proposed in which only cyclohexanone is a reactive substrate leading in parallel to the melange of oxidized products. Cyclooctanone and cyclopentanone are similarly oxidized.

INTRODUCTION

Sodium hypochlorite has been applied in various systems as an oxidizing and chlorinating agent.[1] NaOCl solutions are attractive as industrial oxidants, being cheap, and containing a high percentage of available oxygen (22 wt%).[2] Moreover, the salt solutions resulting from the reactions, are relatively harmless to the environment[3], and can be electrolytically recycled.[4] Developments in the field of Phase Transfer Catalysis (PTC) provide a wider scope of catalytic biphasic systems[5] containing alkali hypohalites. A typical example, developed in our group, is the use of NaOCl as a co-oxidant, together with a homogenous metal catalyst such as $RuCl_3$ (Scheme 1).[6]



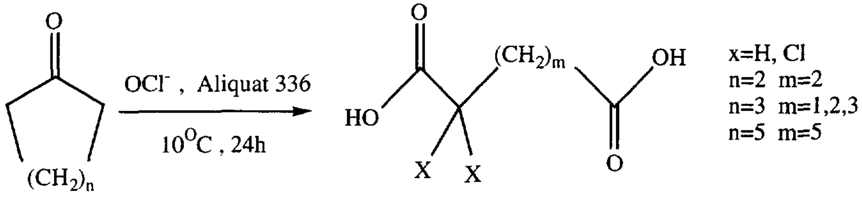
Scheme 1

Previous publications concerning the reaction mechanisms of oxidations by NaOCl in the absence of a metal catalyst are scant.[7] A reaction pathway, incorporating halogenation followed by oxidative cleavage, was suggested for the transformation of propiophenone to benzoic acid.[8]

In one of the largest-scale industrial chemical processes employed today, adipic acid is produced from cyclohexane. In a first step, the cyclohexane is oxidized to a mixture of cyclohexanol and cyclohexanone (KA mixture). In the second step, the KA mixture is oxidized by nitric acid to adipic acid. This second step is fundamentally the same one proposed and patented by DuPont[9] in the 1950's. Today's environmental considerations stress the need to find an alternative oxidation process to replace the polluting nitric acid oxidation route.[10]

RESULTS AND DISCUSSION

We have obtained dicarboxylic acids, in good yields and under moderate conditions, upon oxidation of cycloalkanones with hypochlorite (Scheme 2). Applying an excess of OH^- facilitated the extraction of the reaction products into the aqueous phase, thus simplifying the product separation. Cyclohexanone was used as a model substrate, and the model was found to be consistent with the preliminary results obtained treating other cyclic ketones. Appropriate blank reactions were run in order to verify catalytic and solvent effects. Optimal results were obtained when performing the reaction using the pure ketone substrate itself as the organic phase.



Scheme 2

In a typical experiment, cyclohexanone **1** was reacted for 24h with NaOCl at 10°C in the presence of a catalytic amount (5 mol%) of trioctylmethyl ammonium chloride (Aliquat 336®), to yield adipic acid **2** (69%), glutaric acid **3** (17%), succinic acid **4** (9%), and α,α-dichloroadipic acid **5** (5%); (Fig. 1). α-chlorocyclohexanone **6** and α,α-dichlorocyclohexanone **7** were identified as reaction intermediates in the organic phase. Theoretically, 3 equivalents of hypochlorite are needed to oxidize **1** to **2**, and 5 equivalents are required to obtain **3** or **5**. Since OCl^- itself decomposes under the reaction conditions[13], we found out that 5 equivalents of NaOCl were needed to obtain **2** in optimized yield, with the reaction pH being kept at pH=12 by titrating NaOH, in order to control the relative concentrations of HOCl and OCl^-.

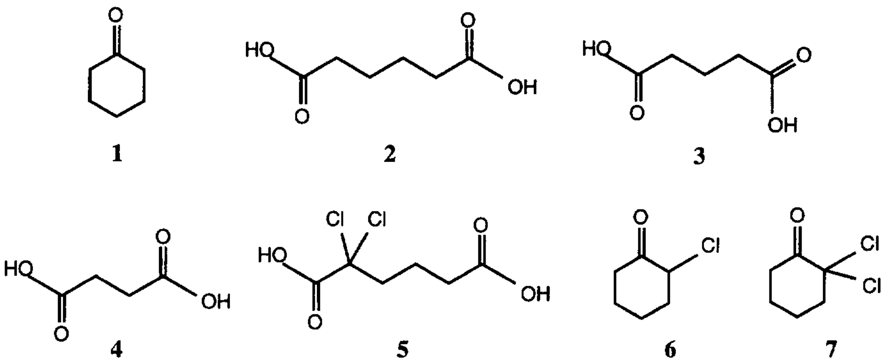


Fig. 1.

Several reactions were carried out under different conditions, the results of which are summarized in Table 1. We observed a remarkable sensitivity of the product selectivity to the acidity of the reaction media (compare product selectivities for entries 8 and 9 on Table 1). This dependency of hypochlorite oxidations on pH has been discussed previously, suggesting an increased extraction of OCl^- at pH=9-10 due to co-extraction with HOCl.[11] Repeated experiments in our system, however, showed that the presence of HOCl promoted the formation of **5** over **2**. The optimal yield[12] of **2** was obtained at pH=12, when $[OCl^-] >> [HOCl]$. HOCl was previously proposed to participate in a free-radical chlorination mechanism[1e] involving ClO•.

Table 1. Oxidation of **1**; Reaction Conditions and Product Selectivity.

			Reaction		% Conv.[d]	% Selectivity[f]			
entry	time (hr)	temp (C)	PTC[a]	pH[b]		**2**	**3**	**4**	**5**
1	2	10	TBAB[g]	10.0	30	41	7	6	46
2	2	10	TBMAB[h]	10.0	30	42	10	5	43
3	24	10	TBAC[i]	10.0	100	49	14	8	29
4	24	10	TBAF[j]	12.5	100	49	11	7	33
5	24	10	$TBAHSO_4$[k]	12.5	100	48	15	11	26
6	2	25	TBMAB	10.0	60	30	10	5	55
7	24	10	TMCAC[l]	10.0	100	55	14	11	20
8	24	10	TMCAC	10.0[c]	100	12	8	5	75
9	24	10	TMCAC	12.0[c]	100	63[e]	17	9	5

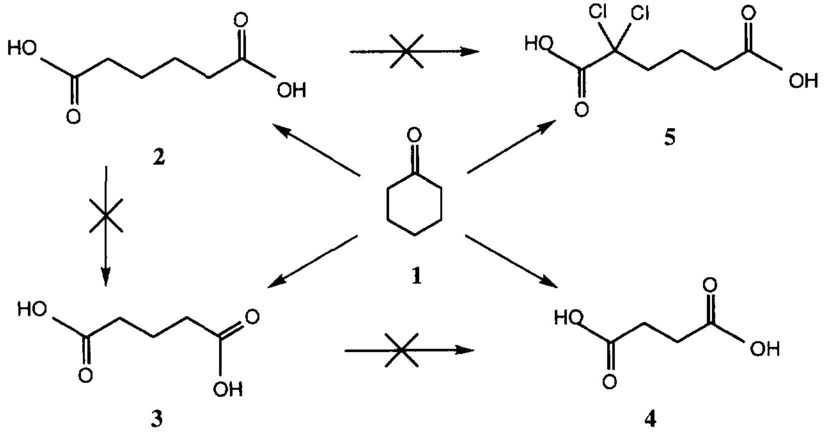
(a) 0.1 molar equivalents; (b) Initial pH (unless otherwise noted); (c) Constant pH; (d) GC conversion (unless otherwise noted); (e) Isolated yield; (f) GC selectivity; (g) Tetrabutylammonium bromide; (h) Tributylmethylammonium bromide; (i) Tetrabutylammonium chloride; (j) Tetrabutylammonium fluoride; (k) tetrabutylammonium hydrogen sulfate; (l) Trioctylmethylammonium chloride.

Studying the catalytic effects of different quaternary ammonium salts, we found that the product selectivity is largely independent of the symmetry and the lypophilicity of the ammonium cation used. Moreover, performing the reaction using ammonium cations paired with counterions of a varying degree of lypophilicity, did not have a sizeable effect on the product selectivity either. These findings can be explained if the organic substrate "sees" practically only the extracted hypochlorite anion[13], which means that the rate of extraction between the two phases is faster than the chemical reaction itself.

NaOCl solutions are known to spontaneously decompose above 30 °C[14], giving Cl_2, O_2 and NaCl. During the reaction, we have measured 85% decomposition of OCl^- after 2h at 25 °C, compared to ca. 60% for reactions performed at 10 °C. Controlling the temperature at 4 °C and 10 °C showed no appreciable difference in the product selectivity. Reactions performed at 25 °C produced various chlorinated organic-phase products, testifying to the existence of competing side reactions at 25 °C.

Cyclooctanone was oxidized by the same method to suberic acid (15% selectivity). dichlorocyclooctanone (45%) was observed in the organic phase. Cyclopentanone was oxidized mainly to **4** (36%) and to α-oxoglutaric acid (22%, assumedly through an α,α-dichloro intermediate).

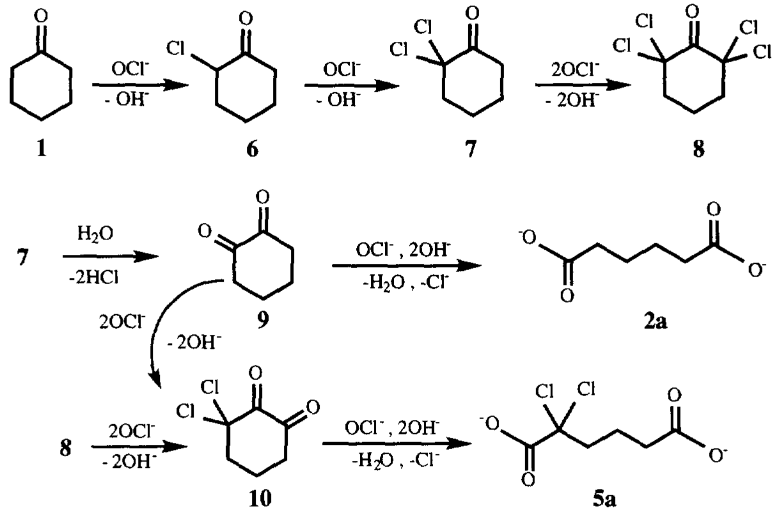
In previous work concerned with the oxidative cleavage of cyclohexanone, **3** and **4** were laconically mentioned as side products.[15] We have realized (Scheme 3), that under the same reaction conditions, only **1** reacted to give **3** (10%) and/or **4** (5%). Similar experiments evidenced that, under the reaction conditions, **2** could not be chlorinated to **5**, nor oxidized to **4**. These findings are important, as they show that the shorter-chained dicarboxylic acids can be obtained (as the deprotonated ions **2a-5a**) *only from the cyclic ketones*.[16]



Scheme 3

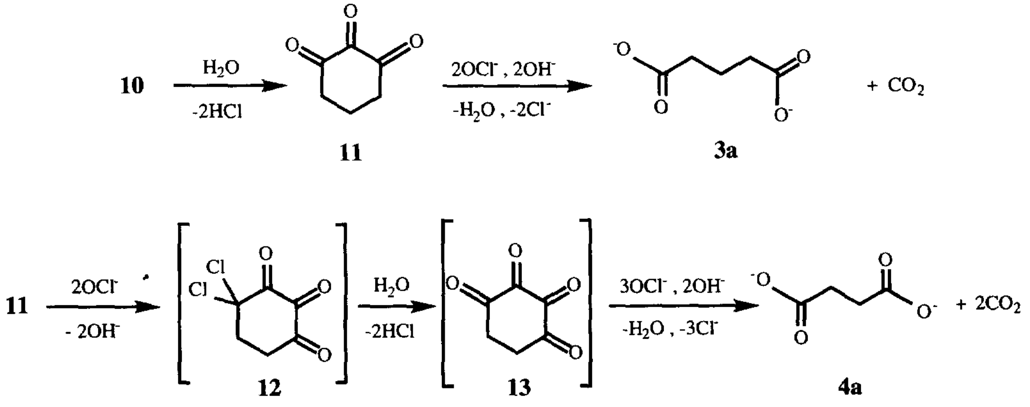
Based on these findings, we propose a reaction pathway for the oxidative cleavage of cycloalkanones, represented by cyclohexanone[17] as a model substrate. As shown in scheme 4, the chlorinating and the hydrolytic reactions compete with each other, depending on the concentrations of HOCl and OCl^-. We have performed separate experiments on 1,2-dioxocyclohexane (**9**, scheme 4), to confirm that this compound undergoes the appropriate reactions depicted to obtain **2a** and **5a**. It was found that in the presence of HOCl, the formation of **10** was faster and the major product was **5a**.

By analogy, cyclooctanone would indeed be expected to yield mainly suberic acid. Cleavage of the 1,2-dioxo species would be faster than in **9**, preventing the formation of shorter-chained and/or dichloro dicarboxylic acids.



Scheme 4

The mechanistic scheme proposed herewith for the formation of **3a** and **4a** (Scheme 5), is based on the fact that both were shown to form directly from the closed-ring species. The intermediacy of **11** was also proclaimed in oxidative ring-cleavage of 1,3 diketones.[18] Supposed compounds [**12**] and [**13**] are proposed by us for the generation of **4a**.[19]



Scheme 5

CONCLUSION

A variation on the well-known Haloform reaction mechanism can explain the oxidative cleavage of cycloalkanones to dicarboxylic acids. Cyclic aliphatic ketones display a higher reactivity then open-chain molecules, and the presence of two sites containing labile α-hydrogens enables diversification of products *via* chlorination and/or hydrolysis. Ion-exchange PTC can be employed to catalyze the reactions. This method enables the pro-environment synthesis of adipic and other dicarboxylic acids, without using metal catalysts or nitric acid. The isolated yield of pure adipic acid was 63%.

EXPERIMENTAL SECTION

General Information

Cyclohexanone, cyclopentanone, cyclooctanone, and 1,2-dioxocyclohexane were purchased from Aldrich Chemical Co. and were used as received. Other chemicals were purchased from Riedel de Haen Chemical Co., and Frutarom Chemical Co. Analytical measurements were taken by GC , GC-MS, and potentiometric titration. pH measurements were taken *in situ* with a pH electrode.

General procedure for the oxidation of cyclohexanone: In a 1L 3-necked round-bottomed-flask, submerged in an ice bath, and equipped with a thermometer, a pH electrode, and a mechanical stirrer, were placed 10.00 grams (1 molar equivalent, 102 mmol) of **1**, and 4.00 grams (0.1 molar equivalents, 10.2 mmol) of Aliquat 336. After the temperature was stabilized at 10°C, 5 molar equivalents (ca. 416 grams of a 10 wt% solution in water) of NaOCl were added. The mixture was then stirred vigorously for 24 hours, during which the pH was maintained at 12.0±0.1 by titrating with 0.5N NaOH. When the organic substrate disappeared, the stirring was stopped. The mixture was extracted with dichloromethane (200ml), the organic phase was discarded and the aqueous phase was acidified to pH=2 with 2M HCl. The flask was left overnight in the ice bath. White needle-like crystals of crude product (3.82 grams) were obtained, filtered, and recrystallized (H_2O, 50°C). A second crop was obtained by evaporating[20] the remaining mixture *in vacuo* (55°C at 25 mmHg), and extracting the solid residue overnight with 100 ml of EtOAc. After filtering off the remaining inorganic salts, the filtrate was evaporated *in vacuo* to give a solid mixture of **2**, **3**, **4** and **5**. From this mixture adipic acid (**2**) was recrystallized. GC-MS data were identical to those of an authentic sample. The overall yield of **2** was 9.40 grams, (mp. 150-152°C lit. 152-154°C), (63 mol% from **1**).

Cyclopentanone and cyclooctanone were oxidized according to analogue procedures.

Aliquat 336 is a registered trademark of Henkel Corp.

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12. Maintaining the pH constant throughout the reaction afforded significant differences in the product yields (mainly between **2** and **5**). In reactions that were allowed to proceed with no pH control, the conditions that were initially imposed by the basic hypochlorite solution changed quickly: Acidic products were formed and extracted into the aqueous phase, thus lowering the pH and shifting the equilibrium towards HOCl. We have found that when both HOCl and OCl^- are present, the chlorination of **9** is faster than the hydrolysis reaction to **2a**. However, the yield of **2** can be maximized by performing the reaction at a *constant* pH of 12, where [HOCl] is negligible.
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16. Traces (less than 1%) of **3** were detected when using **2** as a substrate.

17. Although **6** can undergo under certain conditions a reaction known as the Favorskii rearrangement (March, J. *Advanced Organic Chemistry*; John Wiley and Sons, Inc.: New York, **1992**; pp. 1080-1083) we do not believe this to be the case here, as there is neither an alkoxide ion present, nor were any traces of the rearrangement products detected.
18. Other oxidizing routes using HIO_4 and $Pb(OAc)_4$ can be used to obtain dicarboxylic acids from diols and diketones, going through intermediates of the α,β-dioxo and α,β,γ-trioxo variety. See, for example, Wolfrom, M.L.; Bobbitt, J.M. *J. Am. Chem. Soc.* **1956**, 78 2489.
19. The evolution of CO_2 was confirmed using a $BaCl_2$ solution; Vogel, A.I. *Quantitative inorganic analysis*, 3rd ed.; Longmans: GB, 1962.
20. **CAUTION!** Care should be taken at this stage as some chlorine and carbon dioxide is released from the mixture.

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