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Gif chemistry: new evidence for a non-radical process

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This paper is dedicated to the memory of Professor Sir Derek H. R. Barton (1918–1998)

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Abstract—When performed under a nitrogen monoxide atmosphere, Gif oxidation of cyclohexane with hydrogen peroxide gives no changes in activity or selectivity, showing that triplet oxygen is neither formed nor required in the oxidation. Gif oxidation of *cis*- and *trans*-decalin occurs preferentially at secondary positions giving high yields of ketones. Oxidation of tertiary positions is as low as approximately 5% and probably involves free radicals. Oxidation of cyclohexane in the presence of mannitol gives no significant loss of activity, showing that OH radicals are not involved in Gif oxidation. Based on these results the mechanism of Gif oxidation is discussed. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The particular characteristics of the Gif systems to functionalize saturated hydrocarbons to ketones, preferentially at secondary positions, and the fact that saturated hydrocarbons are preferentially oxidized even in the presence of other more easily oxidizable substances, permitted Barton[1] to attribute to these particular characteristics the name 'Gif chemistry', which he believed to be a non-radical process. Gif chemistry has been explained by the formation of a Fe(V)=O species, formed by the reaction of Fe^{II} with superoxide (Gif^{IV} system) or of Fe^{III} with hydrogen peroxide ($GoAgg^{II}$ system), which then inserts preferentially into the secondary positions of hydrocarbons. The $GoAgg^{II}$ system is the most typical representative of the Gif systems, because it shows high selectivity for ketones and its efficiency with respect to hydrogen peroxide can be as high as 90%, if the reaction is run under a standing inert atmosphere[2] and in the absence of light.[3] Addition of picolinic acid ($GoAgg^{III}$ system) increases the reaction rate by a factor of 40 without changing the Gif characteristics.[4] The $GoAgg^{II}$ oxidation of ^{13}C-enriched cyclohexane monitored by ^{13}C NMR spectroscopy revealed that cyclohexyl hydroperoxide is a major long-lived intermediate.[5] The concentration of this intermediate increases at the beginning of the reaction, but then diminishes as it is transformed into cyclohexanone. Knight and Perkins[6] carried out ^{18}O-labelling experiments in order to investigate whether the oxygen of the product, and consequently the intermediate hydroperoxide, was derived from the hydrogen peroxide or from molecular oxygen. They found that it came substantially from molecular oxygen and proposed that the intermediate hydroperoxide indicates the radical nature of Gif reactions.[7] In his response, Barton[8] showed that radical chemistry could not explain the majority of the characteristics of Gif chemistry. In contrast, the $GoAgg^{IV}$ and $GoAgg^{V}$ systems, which use *tert*-butyl hydroperoxide (TBHP) as oxidant, are certainly of a radical nature.[9–11] A revision of the Gif mechanism proposes that a $Fe^{V}=O$ species inserts into the hydrocarbon bond and that after insertion of O_2 into the iron–carbon bond an alkylperoxo complex is formed, which undergoes hydrogen abstraction at the α position to form the corresponding ketone.[12,13]

The role of molecular oxygen in Gif chemistry is not clear. Passing a flow of argon through a $GoAgg^{II}$ solution strongly suppresses the ketonization of the hydrocarbon.[14] On the other hand, we showed that under a standing atmosphere of argon, the $GoAgg^{II}$ system exhibits better activity and selectivity for the formation of ketones than under air.[2] In this work, we present further evidence that molecular oxygen is not involved in oxidations by the $GoAgg^{II}$ and $GoAgg^{III}$ systems and that free radicals are only formed to a minor extent.

2. Results and discussion

In order to investigate if molecular oxygen is involved, we

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Table 1. Cyclohexane oxidation with the $\text{GoAgg}^{\text{III}}$ system in the absence and presence of NO

t (min)	Cyclohexanone (mmol)		H_2O_2 efficiency (%)[a]	
	Without NO	With NO	Without NO	With NO
5	0.83	0.72	17	14
10	1.40	1.55	28	31
30	1.62	1.80	33	36
90	1.80	1.98	36	40
150	2.02	1.91	40	38

Reaction conditions. 20 mmol cyclohexane, 10 mmol H_2O_2, 1 mmol $FeCl_3{\cdot}6H_2O$ in pyridine (28 mL) and acetic acid (5 mL) at 25°C under a standing atmosphere of air or NO.

[a] Considering the equation: $C_6H_{12}+2H_2O_2 \rightarrow C_6H_{10}O+3H_2O$.

Table 3. Cyclohexane oxidation by the GoAgg^{II} system in the presence of different quantities of D-mannitol

D-Mannitol (mmol)	Cyclohexanone (mmol)	H_2O_2 efficiency (%)
0	1.37	27
1	1.40	28
2	1.48	33
4	1.33	27

Reaction conditions. 20 mmol cyclohexane, 10 mmol H_2O_2, 1 mmol $FeCl_3{\cdot}6H_2O$ in pyridine (28 mL) and acetic acid (5 mL) at 25°C for 8 h.

studied cyclohexane oxidation by the $\text{GoAgg}^{\text{III}}$ system in the presence and absence of nitrogen monoxide (NO), which easily reacts with molecular oxygen and is an OH radical scavenger.[15] As shown in Table 1, the presence of NO does not significantly change either the reaction kinetics or the quantity of cyclohexanone formed (the amounts of cyclohexanol produced were very small). Therefore, we can exclude the presence of OH radicals in the reaction medium and the necessity of molecular oxygen for the formation of the products. Furthermore, it is known that NO reacts with molecular oxygen to form NO_2. Thus, if molecular oxygen was necessary for cyclohexyl hydroperoxide formation, the reaction kinetics and the quantity of oxidized products should have changed.

To prove that NO can really change reaction kinetics, we studied an epoxidation reaction and a radical alkane oxidation under a NO atmosphere. In the epoxidation of cyclohexene, using a molybdenum-silica mixed oxide catalyst and H_2O_2 as oxidant[16] (a typical non-radical reaction), the conversion decreases from 82.5 to 50% in the presence of NO while the selectivity for the epoxide was always better than 95%. In the radical oxidation of cyclohexane, using a chromium-silica mixed oxide catalyst and TBHP as an oxidant,[17] the conversion was significantly reduced from 2.8 to 0.5% and the cyclohexanone/cyclohexanol ratio, which was 10.5 in the absence of NO, decreased drastically to 0.3 in the presence of NO. This shows that the kinetics of the cyclohexane oxidation were totally changed while the kinetics of the cyclohexene epoxidation were only slightly influenced by some NO coordinated to the active sites of the catalyst.

In order to show that free radicals are not involved, we studied the oxidation of *cis*- and *trans*-decalin by the GoAgg^{II} system. The results are presented in Table 2. After 8 h of reaction time both oxidations showed a conversion of approximately 10%. In the oxidation of *cis*-decalin a molar ratio for *cis*-1-, *cis*-2- and *trans*-1-decalone of 4:5:1 was obtained. On the other hand, the formation of *cis*-1-decalone was not observed in the *trans*-decalin oxidation and a molar ratio for *trans*-1- and *trans*-2-decalone of approximately 4:5 was observed. In both oxidations the formation of small quantities of tertiary and secondary alcohols was observed. The ketone/alcohol ratio in *cis*-decalin oxidation was 7:1, while it was 9:1 for *trans*-decalin. Similar results were obtained in a series of three subsequent reactions. A kinetic study showed that the initial rate of *cis*-decalin oxidation is higher than that of *trans*-decalin. This can be explained by the higher reactivity of *cis*-decalin, due to the easy attack at the C(9) and C(10) carbons. After 4 h of oxidation, rates are comparable. The *cis–trans* isomerization, observed for *cis*-decalin, is probably due to the tautomerization of the *cis*-1-decalone in the basic reaction medium, leading to the more stable *trans*-1-decalone. The formation of the tertiary alcohols indicates the participation of radicals in tertiary positions; however, the amounts formed are very small. The molar ratio of *cis*- and *trans*-9-decalol was similar for the oxidation of *cis*- and *trans*-decalin, which suggests the formation of the same radical intermediate. Taking into account the number of C–H bonds, the normalized ratio of secondary to tertiary carbon oxidation is approximately 2:1 for *cis*- and *trans*-decalin, confirming the unusual selectivity of the Gif systems for secondary positions. Using an O_2–H_2O_2–PCA–VO_3^- reagent, where the true oxidant is an OH radical, Shul'pin et al.[18] obtained hydroxydecalins as the major products in the oxidation of *cis*- and *trans*-decalin. The normalized ratio of secondary to tertiary carbon oxidation was 1:4 for *cis*-decalin and 1:2 for *trans*-decalin. Thus, our results show clearly that no OH radicals are involved in the reactions and that no carbon radicals are formed in large amounts.

Cyclohexane oxidation by the GoAgg^{II} system was studied in the presence of ascorbic acid, a well-known OH radical scavenger.[15] Using an ascorbic acid/iron(III) ratio of 1:1, we

Table 2. Oxidation of *cis*- and *trans*-decalin by the GoAgg^{II} system

Substrate	Conversion (%)	*cis*-1-decalone (mmol)	*cis*-2-decalone (mmol)	*cis*-9-decalol (mmol)	*trans*-9-decalol (mmol)	*trans*-1-decalone (mmol)	*trans*-2-decalone (mmol)	Secondary alcohols (mmol)
cis-decalin	9.8	0.65	0.90	0.04	0.07	0.18	–	0.12
cis-decalin[a]	17.5	1.22	1.66	0.06	0.12	0.29		0.16
trans-decalin	9.9	–	–	0.04	0.06	0.79	0.97	0.12
trans-decalin[a]	18.8			0.06	0.08	1.66	1.80	0.18

Reaction conditions. 20 mmol decalin, 10 mmol H_2O_2, 1 mmol $FeCl_3{\cdot}6H_2O$ in pyridine (28 mL) and acetic acid (5 mL) at 25°C for 8 h.

[a] Three portions of 10 mmol H_2O_2 were added in intervals of 8 h.

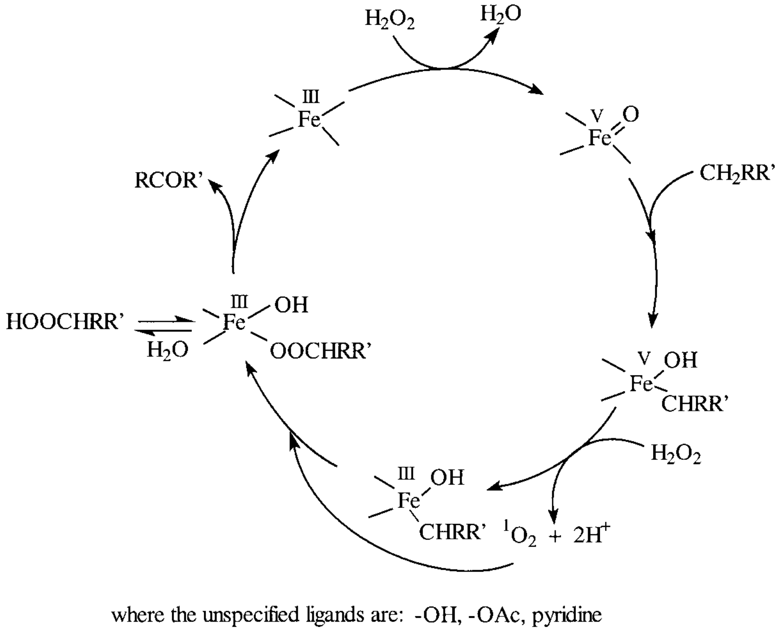

Figure 1. Proposed catalytic cycle for hydrocarbon oxidation by the GoAgg^{II} system.

observed a decrease of 50% in cyclohexanone formation but no change in selectivity. Increasing the ratio to 4:1, the oxidation was strongly suppressed, which we attributed to the complexation of iron(III) by the ascorbic acid.[19] When D-mannitol, which does not coordinate to iron(III), is used as OH radical scavenger,[20] the reaction proceeds normally (Table 3), confirming that no OH radicals are involved in the oxidation.

Based on these results, we would like to present some modifications of the mechanism proposed by Barton et al.[12,13] The catalytic cycle is shown in Fig. 1. Hydrogen peroxide oxidizes the iron(III) complex to iron(V) forming a Fe(V)=O species, which abstracts a hydrogen atom from the hydrocarbon to form an organometallic complex of iron(V). In this organometallic complex the CHRR′-group remains attached to the metal, as found by Mekmouche et al.[21] in the enantioselective hydroxylation of 1,2-dimethylcyclohexane with hydrogen peroxide in the presence of a chiral μ-oxo-diferric complex. The organometallic iron(V) complex then undergoes reduction by H_2O_2 to form an organometallic iron(III) complex and possibly singlet oxygen. The formation of singlet oxygen by the reaction of H_2O_2 with iron picolinate has already been observed by Sheu et al.[22] for the GoAgg^{III} system. The singlet oxygen inserts into the iron–carbon bond to form an organic peroxide, which is coordinated to the iron center. This complex can now undergo hydrolysis, leading to hydroperoxide, or elimination of hydrogen at the α-position, forming the corresponding ketone.

The proposal of singlet oxygen formation is based on the experiments in the presence of NO, which did not show any change in the behaviors of oxidations by the GoAgg^{II} and GoAgg^{III} systems. The participation of hydroxyl radicals was discarded, because the reactions in the presence of D-mannitol, known to be a good OH scavanger,[15] did not show major changes in activity or selectivity. The abstraction of hydrogen by the Fe(V)=O species can occur at secondary or tertiary carbon atoms. However, only in the presence of another hydrogen at the α-carbon atom a rapid decomposition of the alkylperoxo complex to the corresponding ketone is observed. This higher rate of ketone formation explains why secondary C–H bonds are more reactive than tertiary, which would never be expected for radical reactions, as even for the most reactive radicals the normalized ratio of secondary to tertiary carbon oxidation should never be higher than 1.[7]

3. Conclusions

We conclude that Sir Derek Barton was right: Gif chemistry is a non-radical process, which permits the oxidation of saturated hydrocarbons with high selectivity to ketones, even in the presence of other compounds and/or functional groups, which in other systems strongly reduce catalytic activity and change selectivity. However, the presence of pyridine (or a pyridine derivative) and an appropriate carboxylic acid is necessary to maintain Gif characteristics. We believe that Gif chemistry is a valuable tool for oxidizing unreactive CH_2 groups of complex organic molecules, which may contain a wide variety of functional groups.

4. Experimental

Cyclohexane (Aldrich, 99.5%), cyclohexanol (Aldrich, 99%), cyclohexanone (Aldrich, 99.8%), *cis*-decalin (Aldrich, 99%), *trans*-decalin (Aldrich, 99%), 1-decalone (Aldrich, 97%, mixture of *cis* and *trans*), 2-decalone (Aldrich, 95%, mixture of *cis* and *trans*), *cis*-1-decalol (Aldrich, 99%), *cis*-2-decalol (Aldrich, 98%), hydrogen peroxide (Merck, 30% aqueous), pyridine (Aldrich, 99%), acetic acid (Aldrich, 99%), ascorbic acid (Aldrich, 99%), D-mannitol (Aldrich, 99%), picolinic acid (Aldrich, 99%), 1,4-dioxane (Aldrich, 99%), phosphoric acid (Merck, 85%) and $FeCl_3 \cdot 6H_2O$ (Aldrich, 98%) were used as purchased.

NO was generated by the reaction of sodium nitrite with ascorbic acid and bubbled through the reaction mixture of 20 mmol of cyclohexane, 3.0 mmol of picolinic acid and 1.0 mmol of $FeCl_3 \cdot 6H_2O$ in 28 mL of pyridine and 5 mL of acetic acid for 30 min. Aqueous hydrogen peroxide (30%, 10 mmol) was then added and the reaction performed under a standing NO atmosphere at room temperature. Samples were taken at the indicated time intervals and the reaction stopped by the addition of 10 μL of phosphoric acid.

The oxidations of *cis*- and *trans*-decalin by the $GoAgg^{II}$ system were carried out using 28.0 mL of pyridine, 5.0 mL of acetic acid, 20 mmol of the substrate and 1.0 mmol of $FeCl_3 \cdot 6H_2O$. The reactions were started by the addition of 10 mmol of 30% aqueous hydrogen peroxide. After 8 h, 10 μL of phosphoric acid were added to quench the reactions. In subsequent reactions, a new portion of hydrogen peroxide was added to the reaction mixture after 8 h. The cyclohexane oxidations by the $GoAgg^{II}$ system in the presence of ascorbic acid and D-mannitol were performed as described for decalin.

For quantitative analysis, a 1.0 mL aliquot of the reaction mixture was taken and approximately 7.0 mg (with a precision of 0.1 mg) of 1,4-dioxane were added as an internal standard. The mixture was transferred into a 10 mL round-bottom flask in an ice-bath and acidified with 20% H_2SO_4 (v/v) to pH 1. The acidified solution was extracted (3×20 mL) with 1,1,2-trichloro-1,2,2-trifluoroethane and the combined extracts dried with 0.8 g of $MgSO_4$. The filtered extracts were analyzed on a Hewlett Packard 5890 Series II chromatograph equipped with a FID using a Carbowax 20M (25 m×0.2 mm×0.2 μm) column. The carrier gas was helium at $0.25\ mL\ s^{-1}$. For the reactions with cyclohexane the temperature was kept at 55°C for 7 min and then increased at a rate of $40°C\ min^{-1}$ to 200°C. The decalins and their products were isothermally analyzed at 120°C. All products were quantified using calibration curves from authentic samples.

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