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The Selective Functionalization of Saturated Hydrocarbons. Part 36.+ Stereoselectivity Studies of Gif-type Reactions

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Abstract: The stereoselectivity of various Gif-type reactions was evaluated using *trans*-1,4-dimethylcyclohexane as a chemical probe. The results revealed that these reactions were moderately stereoselective. The outcome of the reactions was preferentially formed in the more stable equatorial configuration.

INTRODUCTION

Gif-type reactions are a group of non-heme Fe- and Cu-based chemical models designed to mimic the remarkable oxidizing ability of biological systems.[1] The first significant member of the family was the Gif^{III} system comprising Fe^0 suspended in a mixture of pyridine and acetic acid using dioxygen (O_2) as an oxidant in the presence of H_2S.[2] A more practical system, Gif^{IV} was developed later by substituting Fe powder with Zn powder and employing a catalytic amount of an Fe(II) salt as a catalyst.[3] The use of hydrogen peroxide (H_2O_2) as an oxidant led to the development of three important members namely the $GoAgg^{II}$, $GoAgg^{III}$ and GoChAgg systems. The first two are Fe-based systems, while the latter is a Cu-based model.[4] The oxidation of saturated hydrocarbons by these systems produced ketone as the major component with unusual selectivity. Secondary C-H bonds were found to be preferentially oxidized over the tertiary or primary C-H bonds.[1,5] Moreover, the oxidation of alkanes is not significantly suppressed in the presence of an excess of easily oxidizable compounds such as ethanol, ethylene glycol and even acetaldehyde.[6] In the presence of appropriate trapping reagents, the formation of ketones is diverted to the production of monosubstituted alkyl derivatives.[1] For instance, in the presence of diphenyl diselenide (PhSeSePh) or bromotrichloromethane ($BrCCl_3$), the formation of alkyl phenylselenides and alkyl bromides is detected instead of ketones.[7,8]

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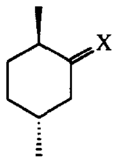
In order to gain a deeper understanding of the mechanistic pathway, the regio- and stereoselectivity of these systems have become crucial characteristics that needed to be carefully evaluated. Among the various substrates studied in Gif-type reactions, adamantane has been extensively investigated and has played a key-role in evaluating the regioselectivity of the system. The adamantane selectivity C^2/C^3 valuederived from various Gif-type reactions was found to be around 1.[9] The C^2 and C^3 are defined as the total oxidized products observed at the secondary and tertiary positions, respectively.

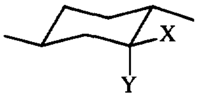
In this article, we wish to present the results of stereoselectivity studies of the various Gif-type reactions using a simple symmetrical hydrocarbon, *trans*-1,4-dimethylcyclohexane as a chemical probe.

RESULTS AND DISCUSSION

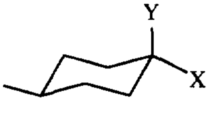
Early studies on the oxidation of *trans*-1,4-dimethylcyclohexane by the Gif^{IV} system have been reported. These were mainly concerned with the regioselectivity of the system, but did not focus on the relevance of stereoselectivity in mechanistic evaluation.[10] The oxidation of *trans*-1,4-dimethylcyclohexane (**1**) by various Gif-type reactions namely Gif^{IV}, GoAgg^{II} and GoAgg^{III} systems is presented in Table 1.



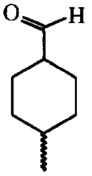
1 $X = H_2$
2 $X = O$



3 $X = OH, Y = H$
4 $X = H, Y = OH$
11 $X = OOH, Y = H$
12 $X = H, Y = OOH$
13 $X = SePh, Y = H$
14 $X = H, Y = SePh$



5 $X = OH, Y = CH_3$
6 $X = CH_3, Y = OH$



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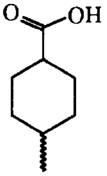

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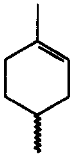

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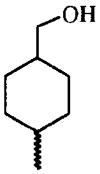

10

Table 1 Comparison of the oxidation of *trans*-1,4-dimethylcyclohexane (**1**) by Gif^{IV}, GoAgg^{II} and GoAgg^{III} systems

Reaction Conditions	Yield (%)*								Σ	C^2/C^3
	1**	**2**	**3**	**4**	**5+6**	**7**	**8**	**9**		
Gif^{IV}	89.3	6.0	0.2	0	1.0	0.6	0	0	97.1	6.20
GoAgg^{II}	84.5	10.9	0.8	0	1.6	0.9	0.4	tr.	99.1	7.31
GoAgg^{III}	76.7	12.6	1.9	tr.	2.1	1.1	0.2	tr.	94.6	6.90

*based on substrate. **recovered substrate. tr. = traces.

The results given in Table 1 show that all of the Gif-type reactions were able to stereoselectively oxidize this substrate (**1**); however, the main product was *trans*-2,5-dimethylcyclohexanone (**2**). Secondary alcohols were detected as minor components, mainly in the equatorial configuration as *trans*-2,5-dimethylcyclohexanol (1,2-*trans*) (**3**). At the tertiary position, it was found that a 1:1 mixture of *cis*- and *trans*- isomers (**5**) and (**6**) was obtained. The formation of this 1:1 mixture implied the possibility of the pathway operating *via* carbon-centered radical, presumably derived from homolytic cleavage of Intermediate A and subsequent reaction with O_2 to produce alkyl hydroperoxide, ultimately giving the tertiary alcohol.[11] However, the amount of activation at the tertiary position was far lower than that observed at the secondary position (C^2/C^3 = 3.93-7.31). The oxidation reaction also took place at the primary position and led to the production of 4-methylcyclohexanecarbaldehyde (**7**) and 4-methylcyclohexanecarboxylic acid (**8**). Another possible compound 4-methylcyclohexanemethanol (**10**), which could in principal be obtained from the oxidation process was not detected. In addition, no alkyl-pyridine derivatives were detected at any position of the molecule.

How does *trans*-2,5-dimethylcyclohexanone (**2**) form?

Previous mechanistic studies have shown that the ketone is derived from the corresponding alkyl hydroperoxide.[11] The formation of the latter was proved to originate from the insertion of O_2 into the C-Fe sigma bonded species (Intermediate A).[11] In the case of the oxidation of *trans*-1,4-dimethylcyclohexane, two possible alkyl hydroperoxides can be formed, either *trans*-2,5-dimethylcyclohexyl hydroperoxide (1,2-*trans*) (**11**) or *trans*-2,5-dimethylcyclohexyl hydroperoxide (1,2-*cis*) (**12**). The stereochemical nature of the alkyl hydroperoxide should in turn reveal the configuration of the C-Fe sigma bonded species (Intermediate A).

As reported earlier, the alkyl hydroperoxide could be quantitatively determined by *in situ* reduction to the corresponding alcohol.[11] Thus, when a variable amount of PPh_3 was added to the Gif^{IV} oxidation reaction of *trans*-1,4-dimethylcyclohexane (**1**), the resulting product distributions were obatined as shown in Table 2. The total activation of the process was found to be constant; however, the ratio of ketone (**2**) to alcohols (**3+4**) at the secondary position decreased markedly. For instance, from 24.0 to 3.6 in the case when 1 mmol of PPh_3 was employed. It was found that the ratio of *trans*-2,5-

dimethylcyclohexanol (1,2-*trans*) (**3**) to *trans*-2,5-dimethylcyclohexanol (1,2-*cis*) (**4**) (equatorial to axial) was around 5.5-6.0 which firmly indicated that C-Fe bond formation preferentially occurred in the more stable equatorial configuration, which then reacted with O_2 to form the alkyl hydroperoxide. The alkyl hydroperoxide was subsequently reduced by PPh_3 to furnish the corresponding equatorial alcohol (**3**).

Table 2 The effect of PPh_3 in Gif$^{\text{IV}}$ oxidation of *trans*-1,4-dimethylcyclohexane (**1**).

PPh_3 (mmol)	Yield (mmol)			$\frac{\mathbf{3}}{\mathbf{4}}$	$\frac{\mathbf{2}}{(\mathbf{3}+\mathbf{4})}$
	2	**3**	**4**		
0	0.24	0.01	0		24.0
1	0.18	0.05	traces		3.6
3	0.14	0.06	0.01	6.0	2.0
5	0.11	0.11	0.02	5.5	0.85

A kinetic study of the Gif$^{\text{IV}}$ oxidation of *trans*-1,4-dimethylcyclohexane (**1**) was performed to observe the ratio of equatorial (**3**) and axial alcohols (**4**) formed. It was found that the ratio of equatorial (**3**) to axial alcohols (**4**) formed along the reaction time scale remained constant with a value of around 5.4-5.8, concomitant with the same ketone to alcohol ratio observed in an independent experiment. A controlled experiment was carried out and revealed that only 14% of the alcohols (**3**, **4**) were oxidized to ketone (**2**). Under Gif$^{\text{IV}}$ conditions, the rate of oxidation of both isomers (**3**, **4**) to the corresponding ketone (**2**) was observed to be constant.

Under GoAgg$^{\text{II}}$ and GoAgg$^{\text{III}}$ conditions, PPh_3 could not be directly applied to the system because of its rapid oxidation by H_2O_2. However, a reductive quenching reaction employing oxalic acid and PPh_3 was successfully performed in the GoAgg$^{\text{II}}$ system allowing observation of the stereochemistry of the derived secondary alcohol.[11] The results are shown in Table 3.

Table 3 Comparative study of the oxidation of *trans*-1,4-dimethylcyclohexane (**1**) under normal GoAgg^{II} and modified work-up with oxalic acid and PPh_3.

Reaction conditions	Yield (mmol)			$\frac{\mathbf{3}}{\mathbf{4}}$
	2	**3**	**4**	
GoAgg^{II} 4 h	0.11	0.02	0.01	2.00
GoAgg^{II} 4 h, modified work-up	0.10	0.15	0.07	2.14

The ratio of *trans*-2,5-dimethylcyclohexanol (1,2-*trans*) (**3**) to *trans*-2,5-dimethylcyclohexanol (1,2-*cis*) (**4**) from the reductive quenching study was found to be 2:1. This clearly shows that there is an intrinsic stereoselective preference for the formation of the C-Fe bond in an equatorial configuration.

Indeed, under GoAgg^{III} conditions, isolation of the crude mixture of alkyl hydroperoxides: *trans*-2,5-dimethylcyclohexyl hydroperoxide (1,2-*trans*) (**11**) and *trans*-2,5-dimethylcyclohexyl hydroperoxide (1,2-*cis*) (**12**) was achieved by utilizing a reductive quenching methodology.[11] Analysis by ^1H NMR spectroscopy clearly revealed that a mixture of alkyl hydroperoxides was present in a 2:1 ratio (equatorial to axial). This observation was in good agreement with the results obtained from the reductive quenching study in the GoAgg^{II} system.

In addition, a study of the effect of PhSeSePh on the oxidation of *trans*-1,4-dimethylcyclohexane (**1**) is presented in Table 4. Applying 5 mmol of PhSeSePh to the Gif^{IV} oxidation clearly revealed the effect of a reducing agent on the system. The ratio of ketone (**2**) to alcohols (**3**+**4**) decreased sharply from 24.0 to 0.83. The ratio of equatorial alcohol (**3**) to axial alcohol (**4**) was found to be 6.0 and was thus in the range observed earlier in the previous study in which PPh_3 was utilized (Table 2). Moreover, the formation of the equatorial phenylseleno derivative; *trans*-2,5-dimethylcyclohexyl phenylselenide (1,2-*trans*) (**3**) was found to prevail over the axial adduct *trans*-2,5-dimethylcyclohexyl phenylselenide (1,2-*cis*) (**4**) by a ratio of 6:1. The preferential formation of the equatorial alkyl phenylselenide was supported by means of ^1H NMR spectroscopy. The crude product clearly showed the presence of *trans*-2,5-dimethylcyclohexyl phenylselenide (1,2-*trans*) (**3**) as a major product of the reaction at the chemical shift around δ 2.76-2.88 ppm (m, half band width 13.0 Hz) in good agreement with the axial proton (**13**, Y = H) of the molecule.[12]

Table 4 The effect of PhSeSePh in Gif^{IV} oxidation of *trans*-1,4-dimethylcyclohexane (**1**).

Reaction Conditions	Yield (mmol)						$\frac{2}{3+4}$	$\frac{3}{4}$	$\frac{13}{14}$
	2	3	4	5+6	13	14			
Gif^{IV}	0.24	0.01	0	0.04			24.0		
Gif^{IV} + PhSeSePh	0.05	0.06	0.01	0.03	0.23	0.04	0.83	6.0	5.8

Therefore, there is no doubt in concluding that the oxidation reactions performed under Gif-type conditions are stereoselctive, preferentially giving equatorial adducts. Moreover, the reactions carried out under Gif^{IV} conditions were found to be more stereoselctive than the corresponding GoAgg systems.

CONCLUSION

The regio- and stereoselectivity study results derived from various Gif-type oxidation systems were found to be different from other oxidation systems and reinforced the non-radical nature of these systems. Evaluation of the stereoselectivity of the systems revealed that Gif-type reactions were moderately stereoselective; the products preferentially formed in the more stable equatorial configuration. Indeed, the reactions performed under Gif^{IV} conditions displayed more stereoselective than those observed from the various GoAgg systems.

EXPERIMENTAL

All chemicals, unless otherwise stated, were purchased as the highest purity commercially available and were used without further purification. Authentic samples of *trans*-2,5-dimethylcyclohexanone[13,14], *trans*-2,5-dimethylcyclohexanol (1,2-*trans*)[14], *trans*-2,5-dimethyl- cyclohexanol (1,2-*cis*)[14], a mixture of *cis*- and *trans*- 1,4-dimethylcyclohexanol[14], 4-methylcyclo- hexanecarbaldehyde[14], 4-methylcyclohexanecarboxylic acid[14], 1,4-dimethylcyclohexene[14] and 1,4-dimethylcyclohexanol[14] were prepared according to previously reported methods and their identities were confirmed by IR, ^{1}H- and ^{13}C-NMR spectroscopy.

IR spectra were recorded on a Perkin Elmer 881 spectrophotometer. ^{1}H and ^{13}C NMR spectra were performed in deuterochloroform with tetramethylsilane (TMS) as an internal reference on a Varian Gemini 200 or Varian XL 200E. Gas chromatography analysis was carried out on a Hewlett Packard 5890 series II instrument, on Chrompack Model 439 or 437S instruments equipped with a flame ionization detector with N_2 as a carrier gas. The columns used for chromatography were DB-WAX (30 m) or DB-5 (15 or 30 m) capillary columns from J&W Scientific (0.32 mm i. d., 25 μm film thickness). Gas chromatography-mass spectrometry (GC-MS) analysis was conducted on a Hewlett-Packard gas chromatograph Model 5790A coupled to a Hewlett-Packard 5970 mass selective detector (40 eV, electron impact). Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel

(Merck, Kieselgel 60 F-254). Column chromatography was performed on silica gel (Merck, Kieselgel 60, 230-400 mesh). Solvents were used either as purchased or dried and purified by standard methods under pure, dry argon.

The oxidation of trans-1,4-dimethylcyclohexane by various Gif-type reactions. The oxidation of *trans*-1,4-dimethylcyclohexane (560 mg, 5.0 mmol) by various Gif-type reactions (Gif^{IV}, GoAgg^{II} and GoAgg^{III} systems) including work-up procedures, the kinetic analysis and the quantification used throughout this work were carried out as those reported previously.[6b,11]

Isolation of a mixture of alkyl hydroperoxides from the GoAgg^{III} system: The GoAgg^{III} oxidation of *trans*-1,4-dimethylcyclohexane (560 mg, 5 mmol) was carried out for 5 min., followed by the addition of oxalic acid (5 equivalents of Fe(III) species used) and an excess amount of PPh_3 (2.62 gm, 10 mmol).[11] The reaction mixture was run further for 15 min and subjected to the usual work-up. The combined ethereal extracts were concentrated to dryness. By means of ^1H NMR spectroscopy, the crude products revealed a mixture of alkyl hydroperoxides present in a 2:1 ratio (equatorial to axial) at chemical shift 3.41-3.55 ppm (half-band width 13.23 Hz) and at 4.03-4.07 ppm (half band width 3.30 Hz) in good agreement with axial and equatorial proton, respectively.[12]

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