Oxidations of Cyclohexanols by N-Bromosuccinimide and Sodium Hypochlorite

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The axial alcohol in *trans*-3, 3, 5-trimethylcyclohexanol was oxidized more readily than the equatorial alcohol in *cis*-3, 3, 5-trimethylcyclohexanol by NBS in aqueous dioxane. On the contrary, the equatorial alcohol was preferentially oxidized to the axial one by 10% aqueous sodium hypochlorite in the presence of tetrabutylammonium hydrogen sulfate (TBHS). The specificity indicates the presence of two different mechanism. In acidic medium, the cleavage of C-H bond is rate determining step while the reactivity of the alcohol is important in the presence of TBHS. The mechanism in basic medium without TBHS will be discussed.

Introduction

Primary and secondary alcohols are oxidized to aldehyde and ketone by N-halogen compound such as N-bromosuccinimide (NBS).[1] One of the most useful application of these compounds has been in the steroid field due to the mildness of the reaction conditions and to the fact that these reagents frequently exhibit remarkable stereoselectivity of particular value in steroid synthesis.[2] In general, equatorial alcohols are more difficult to oxidize than are their axial epimers, and the ease of the reaction is often associated with the solvents as well as oxidizing agents.[3]

Mechanism and kinetics of these oxidations have been reported in the acidic[4] or basic conditions.[5] There are some complexities due to initial oxidation followed by bromination of the product ketone and further reactions in certain cases.[1,6] NBS and sodium hypochlorite were employed to obtain informations on the mechanism of the selective oxidation between equatorial alcohol and axial one.

Experimental

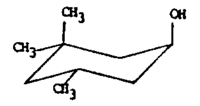
Materials. *cis*-3, 3, 5-Trimethylcyclohexanol and *trans* one were purchased from Tokyo Kasei, and were checked by GLC for purity. The purity of the *cis* alcohol was about 99% and that of *trans* was 97%. The other reagents and solvents are commercial products.

Analytical procedure. The reaction mixture was extracted from ether or ethyl acetate and the solution was analyzed on 6ft x 0.125in. column of 10% carbowax 20M on Chromosorb W with Varian Vista 4600 with FID and CDS 401 data system.

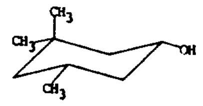
Typical procedure. (1) Oxidation with NBS[7]—*cis*-3, 3, 5-Trimethylcyclohexanol (0.1g, 0.7mmol) was added into the mixture of NBS (0.138g, 0.78mmol), water (1ml) and dioxane (9ml). After stirring for 2hr at r.t., the reaction mixture was treated with aqueous $NaHSO_3$ and extracted from ether; (2) Oxidation with NaOCl—The procedure outlined above was followed using 10% aqueous sodium hypochlorite (2ml, 3.2mmols) and DMF (10ml); (3) Oxidation with NaOCl and tetrabutylammonium hydrogen sulfate (TBHS)[8]—The procedure outlined above was followed using 10% aqeuous sodium hypochlorite (2ml, 3.2mmols), ethyl acetate (10ml) and TBHS (0.05g, 0.35mmol).

Results and Discussion

In order to investigate selective oxidations, *cis*-3, 3, 5-trimethylcyclohexanol and *trans* one were used as an equatorial alcohol and an axial one respectively. The axial alcohol was readily oxidized by NBS within 30 min. in aqueous acetic acid, while the equatorial one was little oxidized. The rate of reaction was generally faster under acidic medium than under basic one.[5]



trans-3,3,5-trimethylcyclohexanol



cis-3,3,5-trimethylcyclohexanol

As shown in Table 1, the axial alcohol was oxidized more readily than the equatorial one in various solvent system. The specificity of NBS oxidation was quite similar to that of chromic acid oxidation.[10]

In the oxidation with sodium hypochlorite as shown in Table 2, the axial alcohol was more readily converted to the corresponding ketone than the equatorial one in aqueous dioxane, MeOH and t-BuOH. But there was one exception that the axial alcohol was oxidized at the almost same rate as the equatorial one in aqueous DMF at *r.t.*[11,12]. When HCl was added into the mixture, the reactivity of the axial alcohol increased while that of the equatorial one decreased sharply. When NaOH was added, both alcohols were difficult to be oxidized. When the oxidation was run in ice bath, the equatorial alcohol reacted faster than the axial one.

Although the reactivity was affected by the acidity of the reaction medium, the selectivity between the axial alcohol and equatorial one did not entirely depend on pH of the solvent. Tetrabutylammonium hydrogen sulfate (TBHS) was used as a phase transfer catalyst (PTC) to increase the reaction rate

Table 1. Oxidation of 3, 3, 5-trimethylcyclohexanol with NBS

No	Alcohol	Condition	Reaction time (hr)	Ketone (%)[9]
1	*trans*	AcOH-acetone-H_2O	1	80.2
2	*cis*	AcOH-acetone-H_2O	1	19.2
3	*trans*	Pyridine	2	30.5
4	*cis*	Pyridine	2	6.2
5	*trans*	Dioxane-H_2O	2	97.3
6	*cis*	Dioxane-H_2O	2	1.4
7	*trans*	Dioxane-H_2O-NaOH[a]	2	42.0
8	*cis*	Dioxane-H_2O-NaOH[a]	2	0.2

[a] NaOH was used in the same equivalent as NBS.

Table 2. Oxidation of 3, 3, 5-trimethylcyclohexanol with NaOCl

No	Alcohol	Condition	Reaction time (hr)	Ketone (%)[9]
9	*trans*	t-BuOH-H_2O	3	6.3
10	*cis*	t-BuOH-H_2O	3	0.5
11	*trans*	Dioxane-H_2O	2	29.1
12	*cis*	Dioxane-H_2O	2	4.8
13	*trans*	DMF-H_2O	1	11.3
14	*cis*	DMF-H_2O	1	10.8
15	*trans*	DMF-H_2O	4	22.6
16	*cis*	DMF-H_2O	4	21.2
17	*trans*	DMF-H_2O,0°	4	24.0
18	*cis*	DMF-H_2O,0°	4	34.4
19	*trans*	DMF-H_2O-HCl[a]	1	32.0
20	*cis*	DMF-H_2O-HCl[a]	1	5.6
21	*trans*	DMF-H_2O-NaOH[b]	1	6.0
22	*cis*	DMF-H_2O-NaOH[b]	1	0.3

[a] 10% aqueous NaOCl was acidified to pH 6 with 10% HCl.
[b] 10% aqueous NaOCl was controlled to pH 13.5 with 10% NaOH.

Table 3. Oxidation of 3,3,5-trimethylcyclohexanol with NaOCl and TBHS[8]

No.	Alcohol	Condition	Reaction time (hr)	Ketone (%)[9]
23	*trans*	H_2O-EtOAc	2	14.6
24	*cis*	H_2O-EtOAc	2	70.5
25	*trans*	H_2O-CH_2Cl_2	2	7.3
26	*cis*	H_2O-CH_2Cl_2	2	12.9
27	*trans*	H_2O-DMF, 0°	1	13.8
28	*cis*	H_2O-DMF, 0°	1	58.7

and to study the selective oxidation.[8,13] 2-Norbornanol did not show different reactivity between *exo* and *endo*. However, the equatorial alcohol in 4-tert-butylcyclohexanol was oxidized more readily than the axial one.[8]

As shown in Table 3, the oxidation rate increased remarkably for the equatorial one and the selective oxidation could be considered to some extent, when TBHS was used in the mixture of water and ethyl acetate. The reactivity of the equatorial alcohol also increased when TBHS was used in aqueous DMF.

From the results of the earlier workers[4,5,6,8] and the present work, the mechanism may be rationalized as shown in scheme 1.

(1) In acidic medium

$$R_2CH\text{-}OH + X\text{-}Y \xrightleftharpoons{\text{fast}} R_2CH\text{-}OY + HX$$

$$R_2CH\text{-}OY + B \xrightarrow{\text{r.d.s.}} R_2C{=}O + HB^+ + Y^-$$

(2) In basic medium

$$R_2CH\text{-}OH + {}^-OY \xrightleftharpoons{\text{r.d.s.}} R_2CH\text{-}OY + OH^-$$

$$R_2CH\text{-}OY + B \xrightarrow{\text{fast}} R_2C{=}O + HB^+ + Y^-$$

(3) With PTC

$$R_2CH\text{-}OH + {}^-OY \xrightleftharpoons{\text{fast}} R_2CH\text{-}O^- + HOY \xrightleftharpoons{\text{r.d.s.}} R_2CH\text{-}OY + OH^-$$

$$R_2CH\text{-}OY + B \xrightarrow{\text{fast}} R_2C{=}O + HB^+ + Y^-$$

X = OH, Br, Cl; B = H_2O, ${}^-OY$, solvent
Y = Br, Cl

Scheme 1. Mechanism of the oxidation reaction in various conditions

In acidic medium, the alcohol reacted with a hypohalite to give the alkylhypohalite and the alkylhypohalite was converted to the corresponding ketone. This mechanism is similar to that of chromic acid oxidation proposed by Westheimer.[14] The rate determining step is the cleavage of the C-H bond.[4] Therefore the axial alcohol reacts faster than the equatorial one. This mechanism can be applied for the oxidations using NBS in various solvent and aqueous NaOCl acidified to pH 6.

In basic medium, the reaction mechanism may be the same as that of acidic medium although the concentration of a hypohalite ion is very low. Otherwise, the rate determining step is not the cleavage of C-H bond, but the reversible nucleophilic attack of a hypohalite ion on the alcohol resulting in the formation of the alkylhypohalite.[5] At any rate, the rate of reaction is quite slow and the axial alcohol also reacts faster than the equatorial one. This explanation was well consisted with the result shown in Table 2.

In the presence of TBHS, a hypohalite ion abstracts the proton from the alcohol resulting in the formation of the corresponding alkoxide and hypohalite. The rate determining step is that the alkoxide ion attacks a hypohalite to give the alkylhypohalite. Therefore the equatorial alcohol is oxidized more readily than the axial one, and the result was well shown in Table 3.

In aqueous NaOCl without TBHS, the reaction can not follow the last mechanism, because the concentrations of the alkoxide ion and a hypochlorous acid are very low.

The oxidation with NaOCl in aqueous DMF was quite different from that in aqueous MeOH, t-BuOH or dioxane. Aqueous DMF can effectively solvates the alkoxide ion compared with other solvents, because DMF reduces the acidity of water to some extent.[15] As lower the reaction temperature, this effect is so important that the reaction comparatively follows the last mechanism as shown in run 17 and 18.

Conclusion

The proposed mechanism is not complete. In acidic medium, the formation of the alkylhypohalite has not been quite understood. Besides, the detailed mechanism of the decomposition of the alkylhypohalite may be open to question depending upon reaction conditions.

The present work emphasizes on the rate determining step. The axial alcohol was oxidized more readily than the equatorial one in acidic medium, while the opposite result was observed in the presence of TBHS and a hypohalite ion.

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9. $$\% \text{ ketone} = \frac{\text{ketone}}{\text{ketone} + \text{unreacted alcohol}} \times 100$$
In certain cases, there were a few peaks in addition to the ketone and the unreacted alcohol. However, the sum of the by-products was less than 2%.
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Aggregation and Dissolution of Cationic Dyes with an Anionic Surfactant

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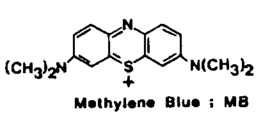
Spectral behaviors of cationic dyes, methylene blue(MB) and acridine orange(AO), with varying concentrations of sodium dodecylsulfate(SDS) were studied. At low concentration of SDS(<1 mM), these dyes formed insoluble dye-surfactant aggregates. When [SDS] is 4-5 mM, the aggregates were dissolved into mixed micelles of constant composition. At higher concentration of [SDS], the composition of mixed micelles were changed with [SDS], resulting only monomeric form of dyes in micelles. AO-SDS system showed greater aggregating and less dissolving properties, and weaker effect of salt than MB-SDS system did. These were attributed to the greater hydrophobic nature of the former dye. The monomer/dimer ratios of dyes in mixed micelles at given [SDS] were greatest at 20°C, reflecting the dependency of CMC of the surfactant on temperature.

Introduction

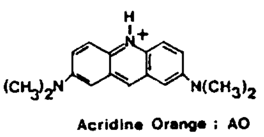
It is well known that surfactants exert profound effects on many chemical reactions and interactions. The effects of surfactants arise mainly from changes in the local environments and concentrations of interacting species due to the interaction with surfactant micelles. In order to elucidate the nature of effects of surfactants and to design desirable surfactant systems, it is essential to understand the nature of interactions between molecules and surfactants.

The dye-surfactant systems have attracted considerable amounts of interest. The enhanced energy transfer between dyes in dye-surfactant systems made them good model membrane systems of chloroplast.[1-4] The peculiar behaviors in both absorption[5-7] and fluorescence[8,9] spectra of dyes in the presence of surfactants of opposite charge were attributed to the formation of a continuum of dye-surfactant aggregates or mixed micelles depending on the surfactant:dye ratio(S/D). The wide range of mixed micelle was also evidenced from hydrolysis kinetic studies of esters of azonaphthol sulfonate dyes in mixed micelles with cationic surfactants.[10,11]

However, the nature of interactions between dyes and surfactants is not known in detail. In this paper, we compared the interaction properties of methylene blue(MB) and acridine orange(AO) with a common anionic surfactant, sodium dodecylsulfate(SDS).



Methylene Blue ; MB



Acridine Orange ; AO

These dyes were chosen because, despite of their structural similarity as shown, they exhibit large difference in their self-associating properties.[12] It was hoped that such intrinsic difference in the associating properties of these two dyes might also be manifested in the interaction with a surfactant and the results would provide valuable information on the nature of dye-surfactant interactions.

Experimental

Sodium dodecylsulfate(SDS) was obtained from Kanto and was recrystallized from ethanol. Methylene blue(Shinyo Pure Chemicals) was recrystallized from 3:1 ethanol-water twice. Acridine orange was obtained from Sigma and used as received. Solutions of MB and AO containing desired amounts of SDS were prepared and kept in the dark overnight. Prior to spectral measurement, the solutions were centrifuged for 10 minutes at 4000 rpm. Concentrations of dyes were calculated from weight data of dyes used to prepare the stock solutions. Absorption spectra were recorded on a Beckman DU-8B spectrophotometer at 25°C using cells of 1 cm pathlength, unless otherwise specified.

Results and Discussion

Both the position and intensity of absorption spectra of MB and AO solutions were varied sensitively with SDS concentrations as shown in Figure 1 and 2. For example, the absorption spectra of 1×10^{-5} M MB exhibited a peak at 660 nm in the absence of SDS. When concentration of SDS was low(<1 mM), the addition of SDS resulted in decrease of the absorbance without noticeable change in the spectral shape. In the range of 1-3 mM SDS, the increasing concentration of SDS had little effect on the spectra. Further addition of SDS