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Selective Reduction of Cyclohexanones with $NaBH_4$ in β-Cyclodextrin, PEG-400, and Micelles

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We report about the selective reduction of eight cyclohexanones with $NaBH_4$ in aqueous solutions of β-cyclodextrin, PEG-400, cationic micelles of CTAB and CPC, anionic micelles of SDS and SS at room temperature and at 80°C. All results were compared with NMR, GC-MS as well as with IR. The charge of the micellar head group influences the preferential direction of hydride attack by favoring one reactant conformation over the other and the outcome is more products with the H^- in the axial position. One example is the reduction of ketone 4. It was obtained 73% of *trans* 4-*tert*-butylcyclohexanol in CTAB, 90% in SDS and 94% in SS micelles. The importance of this work is in the obtained selectivity, the high yields, and the simplicity.

Keywords: Selective ketone reduction; Cyclohexanones; Sodium borohydride; PEG-400; Beta cyclodextrin; Micelles

INTRODUCTION

For over 50 years, sodium borohydride has been extensively used as the reagent for the reduction of ketones to alcohols [1] and for most of this period the remarkable stereoselectivity exibited in the reduction of cyclohexanones has been known. There seems to be an intrinsic preference for axial attack of borohydride when steric hindrance is negligible [2,3]. It has been shown experimentally that the small nucleophiles (such as $LiAlH_4$ and $NaBH_4$) preferentially add to an unhindered cyclohexanone from the axial side to give equatorial alcohol [4]. There is a general agreement that the preferential equatorial attack by bulky reagents or with hindered ketones is due to the steric interference on the axial side [5]. Various hypothesis and models have been proposed to account for the fact that the small nucleophiles add to the unhindered ketones from the axial side [6]. It is about 30 years since Ahn and co-workers pointed out the importance of structure distortion in relation to stereoselectivity [7]. It was stated that the cyclohexanone ring may be flattend so that the attacking nucleophile from the axial side may reach antiperiplanarity with the C_2—H and C_6—H bonds. On the other hand, puckering the ring will destroy this antiperiplanarity. The so-called flattening rule states the following: the more flattened the ring, the more axial attack. Theoretical studies by Houk and coworkers also support this "flattening rule" [8]. Stereoselective reduction is an ever expanding field especially related to the conversion of cyclic ketones to less thermodynamically stable alcohols [9,10], a niche for synthetic methodology that is still lacking acceptable methods [11]. So far, the asymmetric reduction of prochiral ketones has been successfully achieved by using chirally modified metal hydrides [12]. Significant asymmetric induction was obtained by using achiral reagents in a chiral environment [13], various reagents (borohydrides [14], MCRA [15], metal carbonyls [16]), solvent mixtures [17] as well as the additives to $NaBH_4$ (crown ethers [18], metal porphirines [19]) have been used for selective cyclohexanone reduction as well.

Water and aqueous-based solvent systems may represent an increasingly significant choice for the replacement of traditional solvents in synthetic chemistry. Last year a critical review about polyethylene glycol (PEG) and solutions of PEG as a green

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reaction media [20] was published. PEG and its aqueous solutions together with ionic liquids, supercritical carbon dioxide and micellar systems represent interesting solvent systems for solvent substitution. Micelles and cyclodextrins have been used for years as models for enzyme actions [21–25]. Tonelatto said in his review [26] that those two systems do not show any structural similarity (micelles are loosely organized, highly dynamic surfactant assemblies while cyclodextrins are macrocycles) but they are not so different. Both systems, in aqueous media, bind substrates to form superstructures in rapid equilibrium-controlled process and may mediate kinetically-controlled reactions which proceed more efficiently than in bulk solvent. Micelles in water co-micellize the hydrophobic molecules by taking them out of the aqueous phase (the base for their detergency and reactivity). The cyclodextrin macrocycles form inclusion complexes with their substrates (substrates that fit in their 5–8 Å diameter cavity) forming supramolecules which could be defined as a "chiral vessel" due to the large number of chiral carbon atoms in the macrocycle. The processes "catalyzed" by micelles or cyclodextrins are classified according to Bender and Komiyama [23–25] in two categories: covalent and non-covalent catalysis depending on the bonds between substrate and either micelles or cyclodextrines.

The aim of this work was to explore the effect of reaction (micro) media, e.g. the superstructure formation, on the outcome of the hindered (**1**, **5**, **6**, **7** and **8**) and unhindered (**2**, **3** and **4**) cyclohexanone reduction with $NaBH_4$ in the presence of micelles, β-cyclodextrin, and PEG-400 at room temperature and 80°C (Scheme 1).

RESULTS AND DISCUSSION

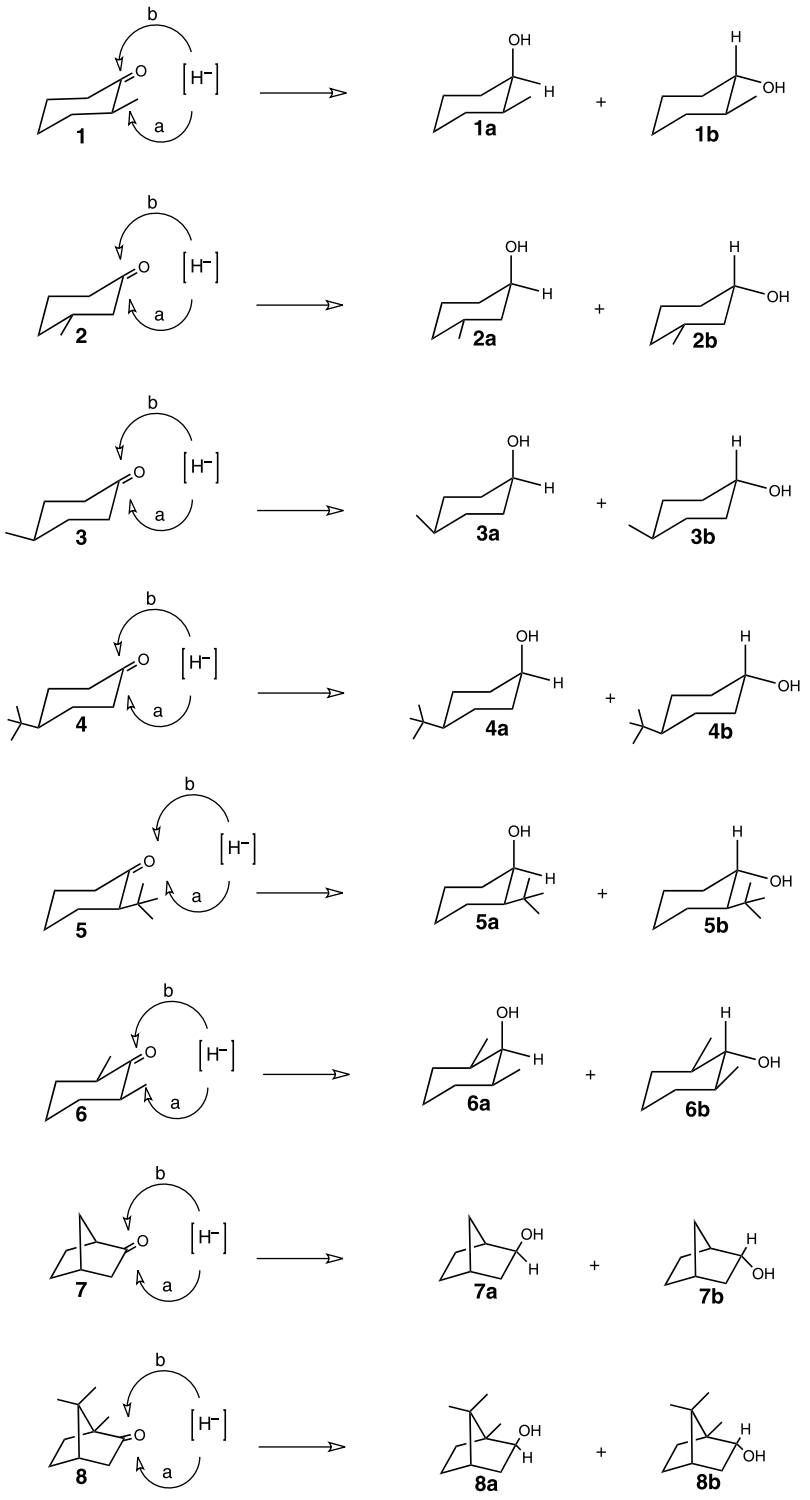
In this report, we describe the use of the different media for the reduction of eight cyclohexanones (**1–8**) with $NaBH_4$. The reductions were performed in aqueous solutions of four surfactant molecules, beta-cyclodextrin and PEG-400. The product analysis was done by using standard identification methods. NMR spectroscopy was the method of choice for the assignation of *cis* and *trans* alcohol formed. GC-MS served for the product ratio determination. IR was used for the check up for the presence of remaining carbonyl group in the reaction mixture and the products' mixtures.

The Reduction in Micelles

It is known that a thermodynamically stabile isotropic solution of a slightly soluble substrate forms due to solubilization in the micelles. Non-ionic, non-polar solutes such us hydrocarbons can be trapped in the hydrocarbon core of the micelle [27]. Other amphiphilic solutes are incorporated alongside the principal amphiphile and oriented radially, and small ionic species can be adsorbed on the surface of the micelle. Since the micellar interior is far from being rigid, a solubilized substrate is relatively mobile. The catalysis of organic reactions by ionic micelles can be explained in terms of electrostatic and hydrophobic interactions of the reactants and activated complexes with the micelle. The reaction substrate is partitioned between micellar and bulk aqueous phases by hydrophobic binding of the substrate to a micelle. The electrostatics in this supramolecular structure attracts or repels an incoming ionic reactant. This study demonstrates one more examples of the influence of hydrophobic interaction on organic reactions [28,29]. In this study four surfactants were examined: two cationic micelles (cetyltrimethylammonium bromide, CTAB; and cetylpyridinium chloride, CPC) and in two anionic micelles (sodium stearate, SS; and sodium dodecilsulphate, SDS). The reactions were performed at various surfactant concentrations, above near and below the cmc for each surfactant (Table I).

Ketones (**1–8**) were reduced in aqueous solutions of CTAB, CPC, SDS, and SS. The reactions were performed at room temperature and at 80°C at nine different concentrations (the main limitation of this approach is that the reactions performed at 80°C favored camphor rather then to sublime before it got all reduced). The reductions performed in CPC gave an undesirable outcome; namely, CPC got reduced forming complicated mixtures. Some products were impossible to isolate by the simple procedures; therefore, those results are omitted. The reaction yields ranged from 80–98% in all three micelles (CTAB, SDS and SS). In diluted micellar solutions the product isolation yields were higher and as the surfactant concentration increased the product isolation yield decreased; namely, some of the compounds stayed associated with the surfactant molecules and salting out could not get them all out. Tables II and III summarize the obtained product distribution upon the reductions of **1–8** ketones in micelles at room temperature and at 80°C.

Our first idea was that maybe the superstructure formation between ketones and micelles could block H^- attack from one side and favor the attack from the other side. Examining the results more closely it could be seen that the reduction of 4-*tert*-butylcyclohexanone, **4**, is sensitive to the change of the micellar head charge the most. The negatively charged tetrahedral transition state of ketone has favorable electrostatic interactions resulting in more axial attack. For all other ketones the effect was less dominant. The steric hindrance of the neighboring methyl groups overcame the micellar charge effect.



SCHEME 1 Possible products formation in the reduction of ketones **1**–**8** with aqueous solutions of $NaBH_4$ in the presence of one of the micelles (CTAB, CPC, SDS, SS), or β-cyclodextrin, or PEG-400 at room temperature and at 80°C.

TABLE I Surfactant concentrations for the various experiments

Surfactant	cmc/M
CTAB	0.0013
SDS	0.0081
SS	0.0018

The reduction of cyclohexanones **1**–**8** with $NaBH_4$ under micellar conditions showed that the selectivity was increased by the surfactant concentration for ketones **1** and **5**. When CTAB was used, for example, the increase of the concentration of the surfactant increased the percentage of the *trans* 2-methylcyclohexanol product due to an axial H^- attack from

TABLE II The product distribution upon the reductions of **1–8** ketones in SDS and CTAB micelles at room temperature. The amount of the left over ketones does not exceed 10% in either case, and it was 0% mostly

	% of product formed upon axial H^-attack							
PAS conc. [moldm^{-3}]	**1b**	**2b**	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**
SDS [4.15x10^{-3}]	67	97	92	89	34	72	83	3
SDS [8.3x10^{-3}]	69	90	89	90	33	71	92	10
SDS [4.15x10^{-2}]	74	89	91	90	57	74	90	5
SDS [8.3x10^{-2}]	72	97	86	90	42	77	91	7
CTAB [5.06x10^{-4}]	60	93	88	–	70	71	–	–
CTAB [9.2x10^{-4}]	65	93	88	–	52	72	–	–
CTAB [5.06x10^{-3}]	70	94	88	–	84	78	–	–
CTAB [9.2x10^{-3}]	76	93	87	–	43	78	–	–

60–76%. We believe that positive charge of the CTAB heads is causing favorable Coulombic attractions with BH_4^- and carbonyl groups at the surface of the micelles making axial H^- attack possible (Fig. 1).

The selective reduction of the conjugated ketones in anionic micelles (SDS) was obtained due to the polarity of the carbonyl group and the orientation in such manner that the carbonyl group remained on the surface of the micelle while the other moiety was inside [30].

The temperature effect was less significant than we expected. Namely, one would think that the thermodynamically stable products would form in greater amount that they did in reality. Table III contains the data for the reduction of ketones **7** and **4** at room temperature and at 80°C. It can be seen that the effect is similar. The reactant gets blocked preferentially in one conformation in micelles favoring the formation of one product.

The Reduction in β-Cyclodextrin

Cyclodextrins provide a chiral site [31] capable of including the guest molecules and are known to induce "template directed" asymmetric reduction of prochiral ketones dissolved or suspended in an alkaline aqueous solutions of sodium borohydride to give the corresponding alcohols in low enantiomeric excess up to 36%.

Our reduction procedure was designed such that the β-cyclodextrin and one of the ketones were mixed and stirred first for 30 minutes before the reductant was added to give enough time to form inclusion complex, superstructure, between the substrate and beta-cyclodextrin. That leg time was determined by UV-vis monitoring of the interaction of particular ketone (the change in the carbonyl group absorption band position) and β-cyclodextrin. Within 30 minutes, all the changes in the band positions occurred. Therefore, our conclusion was that the inclusion complexes were formed [23–25]. Our results (Table IV) point out clearly that the encapsulation within β-cyclodextrin cavity influenced the product formation. Namely, there is a large difference between attack (axial or equatorial) on hindered and attack on unhindered ketones especially when reactions were performed in β-cyclodextrin solutions [32]. In the case of **1**, the inclusion complex formation blocks the equatorial hydride attack, and the result is 86% of *trans* 2-methyl-cyclohexanol product. Ketone **6** yielded even more: 96% of *trans* 2,6-dimethyl-cyclohexanol product.

The Reduction in PEG-400

Some 20 years ago, Santaniello and co-workers [33] reported on a novel reducing system for the selective carbonyl reduction and its inertness toward nitrogen containing functional groups. Sodium borohydride in PEG 400 smoothly reduces carbonyl compounds at room temperature and in this respect behaves similarly to $NaBH_4$ in hydroxylic solvents.

All eight ketones reduced in PEG-400 with $NaBH_4$ yielded more products as a result of an equatorial attack than any of the methods applied in this study. For less hindered ketones (**2**, **3** and **4**), the effect was less than for the hindered ketones. PEG-400:$NaBH_4$ system (with the higher reducing power than $NaBH_4$) favors the kinetically controlled product formation over the thermodynamically controlled products as descriebed in ref. [32]. We could not observe any significant preference for the formation of one kind of product by examining the data obtained for the reductions of ketones **1–8** (Table V). Therefore, the above statement could be applied from case to case and can not be generalized and more study should be done.

CONCLUSION

We can conclude that the selective cyclohexanone reductions with $NaBH_4$ in aqueous solution of micelles, β-cyclodextrin, and 400-PEG was achieved. The formation of a supramolecular structures does influence the reaction outcome but the substrate steric effects dominate regardless the conditions. This is especially observed for the ketones **1**, **5**, **6**, and **8**. When the reaction center is not sterically hindered,

TABLE III The product distribution upon the reductions of **4** and **7** in micelles at room temperature and at 80°C

	Norcamphor, **7**					4-*tert*-Butylcyclohexanone, **4**				
	R.T.		80°C			R.T.		80°C		
PAS conc. [moldm^{-3}]	Ketone% of **7**	Ax/Eq % of **8a/8b**	Ketone% of **7**	Ax/Eq % of **8a/8b**		Ketone % of **4**	Eq/Ax % of **4a/4b**	Ketone % of **4**	Eq/Ax % of **8a/8b**	
SS [1x10^{-3}]	0	95/5	1	99/1		0	10/90	2	3/97	
SS [2x10^{-3}]	0	90/10	0	94/6		0	15/85	6	1/99	
SS [1x10^{-2}]	–	–	0	86/14		0	9/91	2	2/98	
SS [2x10^{-2}]	24	99/0	0	93/7		0	11/89	5	2/98	
SS [1x10^{-1}]	67	100/0	0	95/5		14	6/94	4	7/93	
SDS [1x10^{-3}]	0	88/12	4	97/3		48	9/91	0	18/82	
SDS [2x10^{-3}]	0	86/14	0	84/16		44	1/99	17	10/90	
SDS [1x10^{-2}]	0	90/10	0	93/7		5	1/99	3	13/87	
SDS [2x10^{-2}]	0	95/5	0	94/6		20	2/98	0	11/89	
SDS [1x10^{-1}]	0	87/13	0	74/26		8	32/68	0	36/64	
CTAB [1x10^{-3}]	0	99/1	0	79/21		15	27/73	10	35/65	
CTAB [2x10^{-3}]	0	88/12	0	81/19		19	37/63	20	24/74	
CTAB [1x10^{-2}]	0	88/12	0	75/25		11	45/55	0	35/65	
CTAB [2x10^{-2}]	0	87/13	0	80/20		0	34/66	0	42/58	
CTAB [1x10^{-1}]	0	85/15	0	80/20		0	43/57	0	53/47	

e.g. ketone **4**, than the attraction of the charge of the micellar head and the substrate dictates the product distribution.

The importance of this work is in the obtained selectivity, high yields, and simplicity.

MATERIALS AND METHODS

General

All chemicals were commercial products (Fluka and Aldrich) and used without further purification. The analysis and characterization of the products has been done by: 1. GC-MS (GC Varian 3400 and MS Finningan MAT ITD 800, Column DB1, 30m, Diameter 0.25, carrier gas He); 2. ^{1}H NMR (GEMINI 300 spectrometer; the chemical shifts of NMR are expressed in ppm from TMS as an internal standard, solvent $CDCl_3$) [34]; 3. IR (PERKIN ELMER FT-IR Spectrometer 1725 X; solids were analyzed as KBr pastilles and oils as thin films between NaCl windows).

Procedures

Typical procedure for the reduction (blank reductions in each media were performed following the same procedures but omitting the micelles, cyclodextrin, or PEG-400):

(a) In the micelle (CTAB, SDS, SS): 31.8 g (3.0 mol) Na_2CO_3 and surfactant (various amounts according the listed concentrations in Tables II and III) were dissolved in 500 cm^3 of water. 2.5 mmol of ketone (any one from **1**–**8**) and 10 g (0.3 mol) of $NaBH_4$ were added and the reaction mixture was stirred for 2 days at room temperature. The reaction mixture was saturated with NaCl followed by filtration trough the layer of NaCl and extraction (three times) with diethyl ether. The combined ether extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield an oily residue that was passed trough the short silica-gel column for the removal of any possible remains of surfactant (for the yields see Tables II and III). The product analysis was done by GC-MS, IR, ^{1}H NMR.

(b) In aqueous solutions of β-CD: 2.5 g (2.2 mmol) of β-CD was dissolved in 40 cm^3 0.2 M aq. Na_2CO_3 and 0.75 mmol of ketone (any one from **1**–**8**) was added. The reaction mixture was left to stir for 30 minutes at room temperature and 0.06 g (0.75 mmol) $NaBH_4$ was added. The stirring continues over the night on room temperature. The reaction mixture was

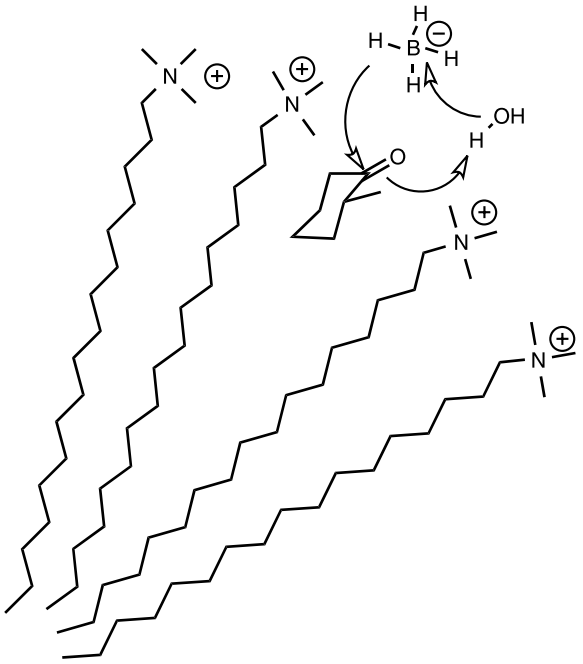


FIGURE 1 Schematic representation of the interaction between the CTAB micelle and the substrate **1**, 2-metylcyclohexanone, during the reduction.

extracted three times with diethyl ether and the combined ether extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield an oily residue that was passed trough the short silica-gel column for the removal of any possible remains of cyclodextrin (for the yields see Tables II and III). The product analysis was done by GC-MS, IR, ^{1}H NMR.

TABLE IV The product distribution upon the reductions of ketones **1–8** in β-cyclodextrin at room temperature

Ketone	% of Axial H^- (product)	% of Equatorial H^- (product)	Left over Ketone (%)
1	86 (**1b**)	14 (**1a**)	0
2	93 (**2b**)	7 (**2a**)	0
3	88 (**3b**)	12 (**3a**)	0
4	100 (**4b**)	0 (**4a**)	0
5	74 (**5b**)	26 (**5a**)	0
6	96 (**6b**)	4 (**6a**)	0
7	93 (**7b**)	7 (**7a**)	0
8	30 (**8b**)	70 (**8a**)	47

TABLE V The product distribution upon the reductions of ketones **1–8** in PEG-400 at 80°C

Ketone	% of Axial H^- (product)	% of Equatorial H^- (product)	Left over Ketone (%)
1	62 (**1b**)	38 (**1a**)	0
2	91 (**2b**)	9 (**2a**)	0
3	80 (**3b**)	20 (**3a**)	0
4	87 (**4b**)	13 (**4a**)	0
5	38 (**5b**)	62(**5a**)	0
6	76 (**6b**)	24 (**6a**)	0
7	88 (**7b**)	12(**7a**)	0
8	36 (**8b**)	64 (**8a**)	20

(c) in PEG-400: In 25 cm^3 of PEG-400 was added 3 g (0.09 mol) of $NaBH_4$ and heated at 80°C. 0.005 mol of ketone (any one from **1–8**) was added to the reaction mixture and stirred for 2 hours. The mixture was left to cool down to room temp and 2 M HCl was added. The mixture was poured over 300 $cm^3$of water and extracted three times with diethyl ether. The combined ether extracts were dried over the anhydrous Na_2SO_4. The solvent was removed under the reduced pressure to yield an oily residue that was passed trough the short silica-gel column for the removal of any possible remains of surfactant (for the yields see Tables II and III). The product analysis was done by GC-MS, IR, ^{1}H NMR.

Acknowledgements

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