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Highly Regio- and Stereoselective Reductions of Carbonyl Compounds in Aqueous Glycosidic Media

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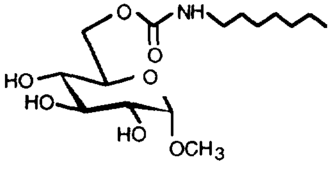
Abstract : Highly regioselective reductions of α,β-unsaturated ketones to the corresponding allylic alcohols were performed in essentially quantitative yields in aqueous media containing either glycosidic surfactants or amphiphilic carbohydrates. Reductions of cyclohexanones and cyclohexenones lead under the same conditions, stereoselectively to reduced compounds bearing an equatorial alcohol function. Hydrophobic interactions between amphiphilic carbohydrates and lipophilic substrates were modelized and should account for the observed stereodifferentiation.

Organic synthesis in aqueous media has attracted growing attention in the past few years.[1] Unfortunately only a few organic compounds display sufficient solubility in water. The use of glyco-organic substrates, which contain a carbohydrate moiety enhancing water solubility and inducing chirality, was thus extensively studied.[1] However easy cleavage of the sugar moiety is a requisite for obtaining the final product. Alternatively, incorporation of the substrate and/or reagent molecules into micelles, microemulsions and various organized assemblies may enlarge the field of organic aqueous reactions.[2] Indeed, micellar aqueous solutions of surfactants proved recently to enhance both the rate and the enantioselectivity of asymmetric hydrogenations promoted by water-soluble rhodium catalysts based on carbohydrates.[2d] In this paper, we would like to report on highly regio- and stereoselective reductions of a wide range of carbonyl compounds by sodium borohydride in aqueous solutions containing glycosidic amphiphiles. Our results will be compared with other findings based on the water structure strengthening effects exerted by sugars such as D-glucose.[3]

In order to enhance the solubility of ketones in aqueous media and to localize the substrates , reactions were carried out either i) in micellar solutions of selected non ionic glycosidic surfactants **A**[4] and **B**[5] or ii) in aqueous solutions of amphiphilic carbohydrates **C**-**E**.[6] Hecameg **A** [4] and dodecanoyl-β-D-maltoside **B** [5] proved to be soluble in water at concentrations up to 0.2 M and were expected to be stable under our reaction conditions. Critical micellar concentrations of 19.5 mM [4] and 0.38 mM [7] were found respectively for **A** and **B** in a phosphate buffer. Methyl-β-D-galactoside **C** and L-arabinose **D** are characterized by an arrangement of hydroxyl and methine groups which divide the molecules into hydrophilic and hydrophobic areas and thus display amphiphilic structures [6c].

The behaviour of sucrose **E** in water or polar organic solvents is more controversial [8-10] but most chemists now agree that the 2-oxygen of the glucopyranose moiety acts as an hydrogen bonding acceptor for either 1'-OH or 3'-OH of the fructose ring,[8,9] thus maintaining the two rings approximately at right angles and creating an hydrophobic region in the fructose part of sucrose.[11] We thus anticipated that apolar solutes may undergo energetically favorable hydrophobic interactions with the hydrophobic portions of these carbohydrates.



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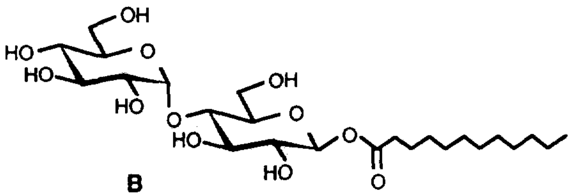

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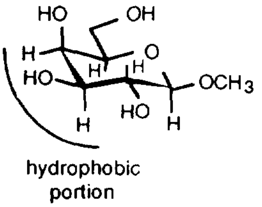

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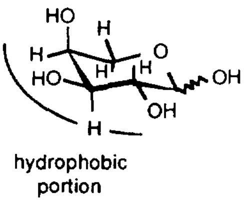

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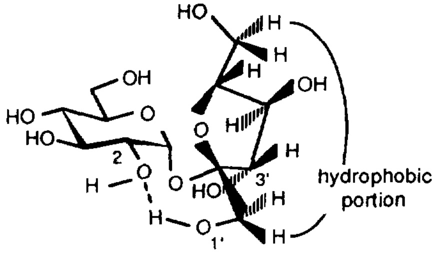
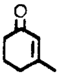


E

Reductions of enones (1.6 mmol) were carried out at room temperature with sodium borohydride (3.2 mmole) in aqueous 0.2 M solutions of **A**, **B** (20 mL) or M solutions of carbohydrates **C**-**E** (20 mL). The reactions were stirred for 12 hr at room temperature. The products were extracted with diethyl ether and their purity was determined by capillary GLC analysis. The main results listed in Table 1 show that reductions of cyclohexen-2-ones **1**-**4** and benzylideneacetone **5** were nearly quantitative under the conditions described herein. The regioselectivity of the reaction was dramatically enhanced towards the 1,2-reduction leading to the corresponding allylic alcohols when compared with the selectivities attainable in alcoholic and ether solvents,[12] in water in the presence of cyclodextrines[13] or water structure strengthening carbohydrates, e.g. methyl α-D-glucoside.[3] It is noteworthy that complete chemoselectivity was observed in the case of compound **4** bearing both enone and α,β-unsaturated ester functions. These results suggest that alkoxyborohydrides derived from carbohydrates are involved in these reactions enhancing the attack of hydride at the hard site i.e. carbon 1 of the conjugate enone system.[15] Nevertheless the regioselectivity of the reduction of 2-pentylcyclopent-2-enone **6** was lower than in the case of cyclohexenones, highlighting that cyclopentenones are more prone to conjugate addition than cyclohexenones.[14]



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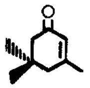

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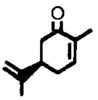

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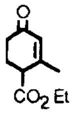

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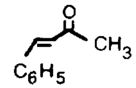

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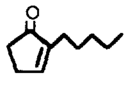

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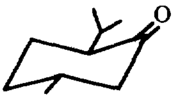

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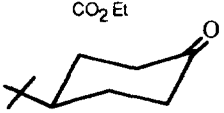


8

Table 1 : Regioselective reductions of α,β-enones with $NaBH_4$ in aqueous media.

Substrate	Additive	% of conversion (a)	Isolated yields (%)	% of selectivity (a) 1,2 : 1,4	% of selectivity using $NaBH_4$ in methanol
1	**A**	100	94	65 : 35	56 : 44
1	**E**	100	93	96 : 4	
2	**A**	100	87	88 : 12	76 : 24
2	**C**	98	86	97 : 3	
3	**C**	98	95	98 : 2	63 : 37
3	**E**	99	93	99 : 1	
4	**C**	100	95	> 99 : 1	82 : 18
4	**D**	100	96	> 99 : 1	
4	**E**	100	94	91 : 9	
5	**A**	100	98	> 99 : 1	100 : 0 [2a]
6	**A**	64	60	79 : 21	42 : 58

(a) Product purity was determined by capil96lary GLC measurements.

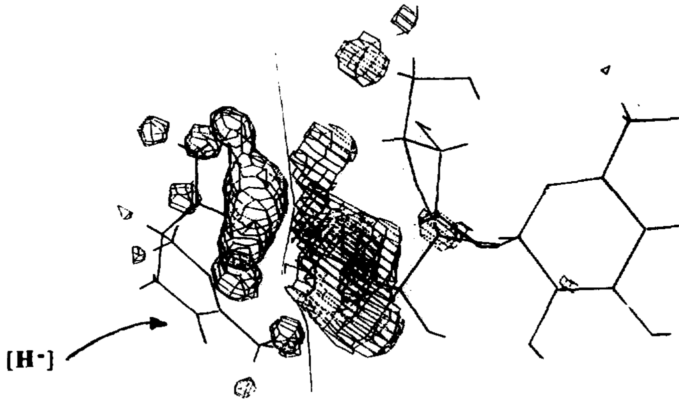
The next step was to ascertain that carbohydrates or their derivatives would be helpful for stereodiscrimination in the reduction of carbonyl compounds. Our results for the reduction of representative cyclic ketones in the presence of carbohydrate derivatives are summarized in table 2. The data shows that the present method is of general applicability for α,β-unsaturated and saturated substrates. $NaBH_4$ in aqueous glycosidic media reduced ketones **4** and **7** to the equatorial alcohols with 79 and 72 % selectivities, respectively, whereas lower selectivities have been recently found by using complex reagents under non aqueous conditions.[16] In the case of (-)-carvone **3** and 4-*tert*-butylcyclohexanone **8**, a dramatically enhanced axial entrance of the hydride was demonstrated since 93 % of (-)-*cis*-carveol and 98 % of *trans*-4-*tert*-butylcyclohexanol was obtained respectively. These results therefore represent a substantial improvement over conventional methods.[12]

Table 2 : Stereoselective reductions of cyclic ketones with $NaBH_4$ in aqueous media.

Substrate	Additive	% of conversion (a)	Isolated yields (%)	% of stereoselectivity (a)
3	**E**	99	93	cis : trans ; 93 : 7
3	**A**	80	75	cis : trans ; 93 : 7
4	**E**	100	94	trans : cis ; 68 : 32
4	**D**	100	96	trans : cis ; 79 : 21
7	**B**	89	87	eq : ax ; 72 : 28
8	**B**	89	88	trans : cis ; 98 : 2
8	**E**(b)	96	90	trans : cis ; 93 : 7

(a) Product purity was determined by capillary GLC measurements; (b) This reaction was carried out at + 50°C.

The observed facial discrimination suggests that hydrophobic interactions may be involved between the hydrophobic portions of amphiphilic carbohydrates and those of cyclic ketones.[17] Our initial attempts to calculate [18] the hydrophobicity potentials [19] allowed unequivocal correlations between the hydrophobic contact surfaces of carbohydrates and those of substrates, *i.e.* the fructosyl portion of sucrose **E** and the *Re* face of L-carvone **3** (see scheme 1). We assume that a subsequent attack of the reducting species on the *Si* face of L-carvone can thus take place. Progress in this area based on aggregation of lipophilic substrates with amphiphilic carbohydrates will be reported in due course.



Scheme 1-Hydrophobic potential isolevels for sucrose **E** and L-carvone **3**.[18]

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