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Stereoselective Reduction with Sodium Dithionite of Conjugated Enones in the Presence of β-Cyclodextrin and Its Heptakis(2,6-di-*O*-methyl) Derivative as Host Compounds or Phase Transfer Agents

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Abstract. The reduction with sodium dithionite in aqueous alkaline solution of the conjugated carbon–carbon double bond of carbonyl compounds **1–5** as inclusion compounds in β-cyclodextrin (CD) and its heptakis(2,6-di-*O*-methyl) derivative (DMCD) has been investigated. These results are compared with those obtained under phase transfer conditions (1 : 1 water–toluene) using methyltrioctylammonium chloride or DMCD as transfer agents. Remarkable kinetic effects as well as regio- and stereoselectivities were observed, depending on the nature of the host molecule and of the substrate.

Key words: Cyclodextrin, inclusion complexes, conjugated enones, reduction, phase transfer.

1. Introduction

The two main reduction modes of α,β-unsatured aldehydes and ketones involve formal hydride attack at either the C-1 or C-3 carbon atoms of the enone system, leading to the formation of allylic alcohols or saturated carbonyl compounds, respectively. Moreover, depending on the experimental conditions used, the reaction may proceed further, involving formal addition of two or three hydrogen molecules, to yield the corresponding saturated alcohols or the saturated hydrocarbons.

In the past fifty years [1] these reactions have been extensively investigated and the results obtained were found to be strongly affected by a variety of factors, e.g. by the nature of the reducing agent and of the substrate, the presence of a catalyst, the nature of the solvent. The search for optimum conditions for regio- and stereoselectivity is still a challenge. In a previous work [2] we reported on the competition between 1,4- and 1,2-reduction of the conjugated enone (*R*)-(−)-carvone, using sodium dithionite as reducing agent, in aqueous sodium hydrogen carbonate and in the presence of native and modified cyclodextrins. The results

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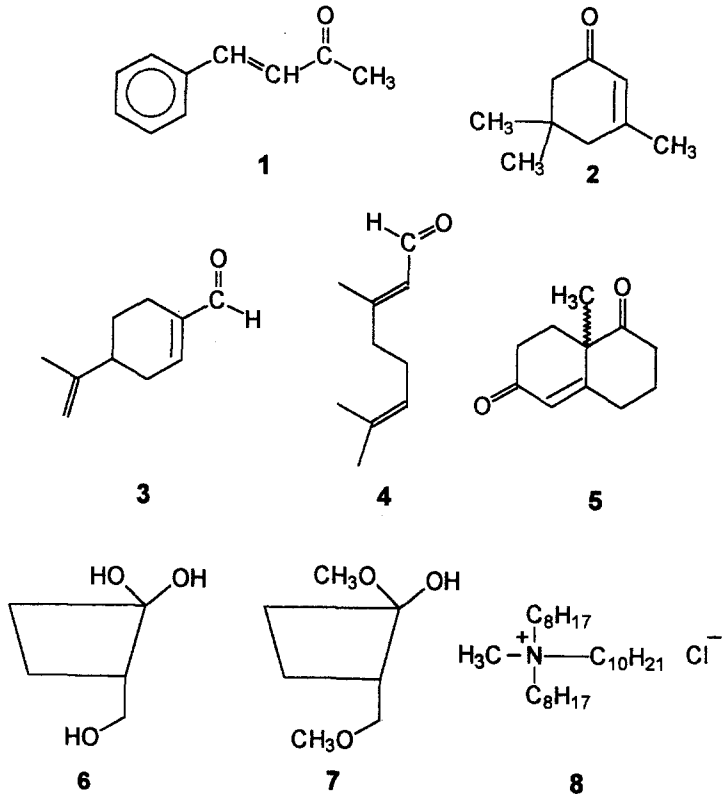


Chart 1.

obtained indicated that the system used was rather versatile, giving good selectivity under the proper experimental conditions, easy work-up of the reaction mixture and satisfactory yields of the products with use of low cost reagents.

As an extension of this work, we have investigated the reduction of carbonyl compounds **1–5** in the presence of native β-cyclodextrin **6** (CD), and its heptakis(2,6)-di-*O*-methyl derivatives **7** (DMCD) in aqueous solutions of sodium dithionite at 80°C. The interesting results obtained in preliminary experiments carried out for the sake of comparison, stimulated us to investigate the reduction of selected substrates also in a 1 : 1 toluene–water mixture using as phase-transfer agents the ammonium salt **8** (Aliquat 336) and DMCD **7**. The substrates chosen for this study are rather different in structure (see Chart 1), but in any case they possess a hydrocarbon structure suitable to form inclusion complexes in CD or DMCD, as shown from inspection of the CPK molecular models.

2. Experimental

Solvents, cyclodextrins and compounds **1–5** were all commercial products and have been purified by standard procedures. Aqueous solutions were prepared using twice distilled water.

^{1}H-NMR spectra were recorded in $CDCl_3$ or Me_2SO-d_6 solutions (internal standard Me_4Si) on a Bruker WP 200 SY instrument. GC-MS measurements were performed with a Hewlett-Packard 5970 instrument, equipped with a polydimethylsiloxane column (12 m × 0.25 mm i.d; Alltech). Circular dichroism spectra were recorded in aqueous solution with a JASCO J-500-A spectropolarimeter equipped with a DP-501 data processor and a cylindrical 1 cm fused-quartz cell. GC analyses were performed on a Varian 3700 instrument equipped with a Carbowax 20 M 15% on Chromosorb WAW-DMCS 150 cm column.

The inclusion complexes of **1–5** with CD and DMCD were precipitated from an aqueous solution of the receptor upon addition of one equivalent of the guest molecule. The white solid obtained was filtered, washed with diethylether and dried over P_2O_5. In all cases, the 1 : 1 stoichiometry of the inclusion complexes was ascertained by ^{1}H-NMR in Me_2SO-d_6.

The general reduction procedure was as follows. An aqueous solution (100 mL) containing $NaHCO_3$, $Na_2S_2O_4$, and the preformed inclusion complex (1 mmol), in the molar ratio 18 : 9 : 1 was heated at 80°C, under a nitrogen atmosphere and vigorously stirred. Virtually the same results were obtained when the substrate and CD or DMCD in a 1 : 1 ratio were separately added to the solution, instead of the preformed complex. After the desired time, the reaction mixture was cooled and extracted with diethylether. The organic layer was then dried and the solvent evaporated under reduced pressure. GC analysis of the residue allowed the determination of the nature and relative amounts of the reaction products. These were finally separated by column chromatography on silica gel, using suitable eluants and identified through their spectroscopic properties and/or by comparison with authentic samples.

Phase-transfer experiments were carried out by adding to a 1 : 1 water–toluene mixture (100 mL), $NaHCO_3$, $Na_2S_2O_4$ and the substrate (1 mmol) in the molar ratio 18 : 9 : 1, as above, together with either CD (1.1 mmol) or DMCD (1.1 mmol) or **8** (0.3 mmol), followed by standard work-up of the reaction mixture. Under these conditions, preliminary experiments carried out at room temperature, indicate that whereas CD is virtually absent in the organic phase, approximately 40% of the total DMCD resides in toluene.

3. Results

3.1. Reduction of 4-phenyl-but-3-en-2-one **1**

The products obtained in the reduction of **1** with dithionite, under various conditions, are indicated in Chart 2 and their yields (%), as determined by GC analysis,

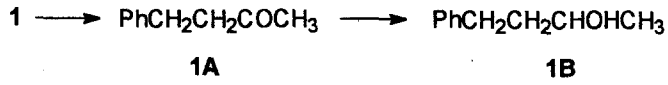


Chart 2.

TABLE I. Reduction of 4-phenyl-but-3-en-2-one, **1**

Entry	Reaction time (h)	Additive	**1A** %	**1B** %
1	3	–	2	–
2	3	**6** (CD)	11	3
3	3	**7** (DMCD)	2	–
4	3	**8** (A 336)[a]	18	3

[a] In water/toluene.

are reported in Table I. The reduction without any additive (entry 1) is rather slow and, after 3 h, affords ketone **1A** as the only product, in very low yield.

The reduction of **1** in the presence of CD (entry 2) proceeds faster and yields a mixture of the ketone **1A** and of the alcohol **1B** (as a racemic mixture). Virtually the same results were obtained under phase transfer conditions using **8** (entry 4), which are comparable with those reported by Camps *et al.* [3] under similar conditions. On the other hand, DMCD is totally ineffective (entry 3).

3.2. Reduction of Isophorone **2**

The observed reduction products of isophorone **2** are indicated in Chart 3 and the results obtained in the absence and in the presence of additives are shown in Table II.

This reaction, too, proceeds remarkably faster in the presence of CD than it does without additives. After 3 h (entry 2), the saturated ketone **2A** was isolated, as racemic mixture, in satisfactory yield, together with a mixture of diastereomeric alcohols **2B** and **2C**; after 8 h (entry 3) the overall yield of reduction

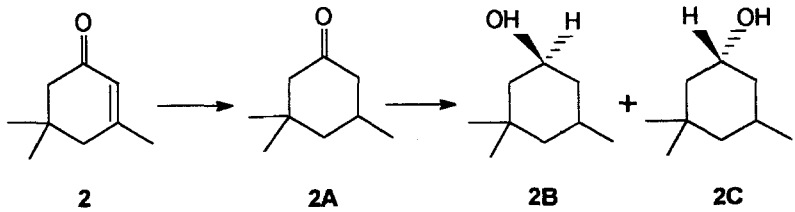


Chart 3.

TABLE II. Reduction of Isophorone **2**

Entry	Reaction time (h)	Additive	**2A**[a] %	**2B** + **2C**[a] %
1	3	–	9	–
2	3	**6** (CD)	61	1
3	8	**6** (CD)	65	25
4	3	**7** (DMCD)	4	–
5	3	**8** (A 336)[b]	61	4
6	8	**8** (A 336)[b]	84	10

[a] As a racemic mixture.

[b] In water/toluene.

products increases, due mainly to the larger amount of alcohols formed and the ketone/alcohol ratio decreases.

The results observed under phase transfer conditions (entries 5 and 6) resemble those obtained in the presence of CD and are in agreement with those reported by Camps [3]; however, it may be noticed that, under these conditions, the reaction yields, after 8 h, a larger ketone/alcohol ratio with a higher amount of ketones formed. In the presence of CD, the second reduction step (i.e. the conversion of ketones to alcohols) proceeds at a higher rate than under phase transfer, yielding up to 25% of the saturated alcohols with a diastereomeric ratio **2B/2C** = 20/80, as determined by ^{1}H-NMR analysis of the mixture. It is noteworthy that such a ratio was found to be inverted in the reduction of ketone **2A** with $NaBH_4$ in ethanol [4]. Finally, the presence of DMCD (entry 4) slows down the reduction and only a small amount of saturated ketone is recovered. The quite different results obtained using CD and DMCD as host molecules prompted us to carry out induced circular dichroism (i.c.d.) measurements of the aqueous solutions of the inclusion complexes formed between **2** and both CD and DMCD. The i.c.d. spectra (see Figure 1) show a negative band in both cases. Following Uedaira's studies [5], the negative sign of the i.c.d. band generally indicates an axial mode of insertion, whereas a positive band would indicate an equatorial inclusion of the substrate within the complex. Thus, the mode of insertion of **2** is apparently similar in both the macrocyclic host systems, in spite of the different chemical reactivity observed.

3.3. Reduction of *S*(−)-4-(1-methylethenyl)-cyclohexene-1-carboxaldehyde (perryllaldehyde) **3**

Chart 4 shows the products of partial (aldehydes **3A** and **3B**) and full reduction (alcohols **3C** and **3D**) of perryllaldehyde **3**. The results obtained are reported in Table III.

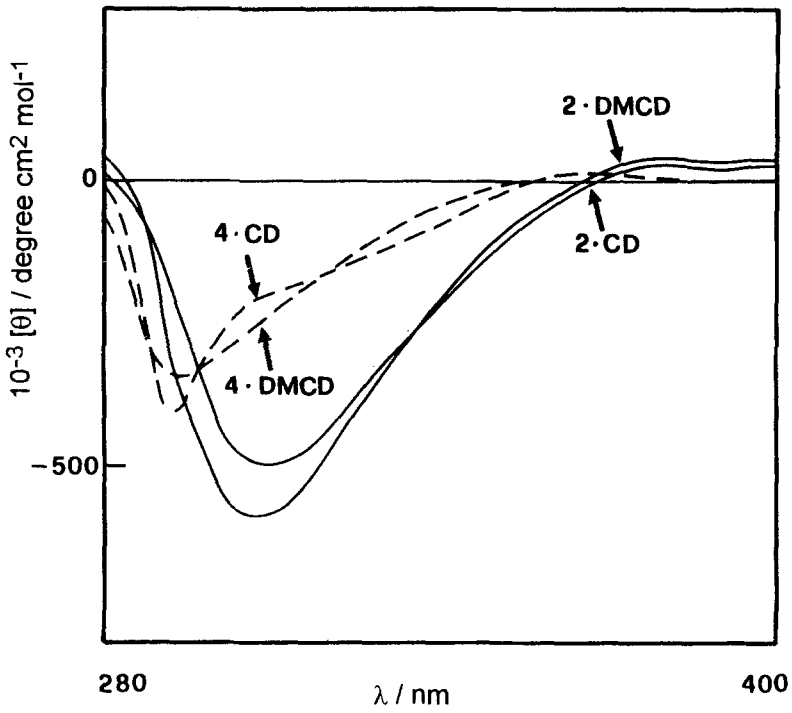


Fig. 1. I.c.d. spectra of complexes of **2** and **4** with β-CD and DMβ-CD.

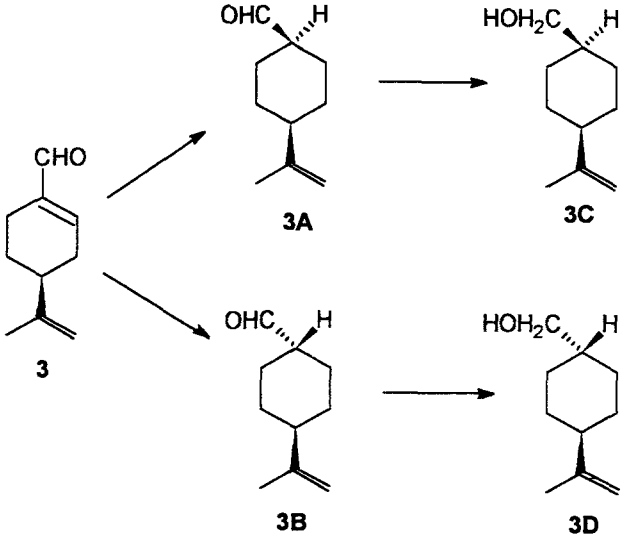


Chart 4.

TABLE III. Reduction of Peryllaldehyde **3**

Entry	Time (h)	Additive	**3A + 3B**[a] %	**3C + 3D** %
1	4	–	16 (70/30)	17
2	0.5	**6** (CD)	45	15
3	3	**6** (CD)	7 (10/90)	84
4	2	**7** (DMCD)	8	2
5	2	**7** (DMCD)[b]	40 (70/30)	–
6	4	**8** (A 336)[b]	52 (70/30)	46
7	8	**8** (A 336)[b]	15 (70/30)	83

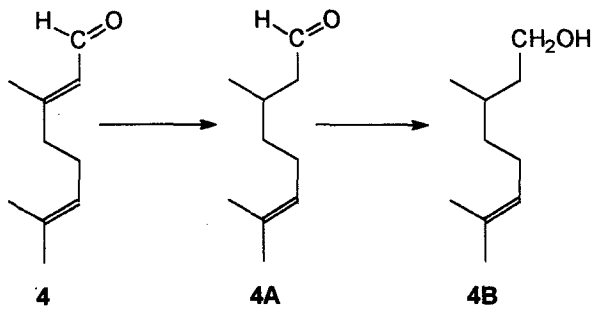
[a] Diastereoisomeric ratio **3A/3B** in parenthesis, as determined by ^{1}H-NMR.
[b] In water/toluene.

In the absence of additives (entry 1) the reduction of **3** yields, after 4 h, comparable amounts of aldehydes (**3A** + **3B**) and alcohols (**3C** + **3D**) in moderate yield. The reaction is considerably faster in the presence of CD (entries 2 and 3): after 30 min, a 60% conversion of **3** is observed, and the aldehydes and alcohols are obtained in good yield; after 3 h, the major products are the alcohols **3C** and **3D**; the aldehydes are present in small amount with an inverted diastereomeric ratio (**3A/3B**=10/90) with respect to that found in the absence of CD and under phase transfer conditions (*vide infra*). In aqueous solutions, DMCD slows down the conversion (entry 4) whereas, under phase transfer conditions, (entry 5) it gives, after 2 h, satisfactory yields of the aldehydes and, quite remarkably, without the formation of the corresponding alcohols. On the other hand, under phase transfer conditions using **8** (entries 6 and 7), comparable amounts of aldehydes and alcohols are obtained after 4 h, while, after 8 h, the alcohols are the major products of the reaction.

3.4. Reduction of 3,7-dimethyl-2,6-octandienal (citral) **4**

Citral **4** may be reduced first to citronellal **4A** and then to citronellol **4B** as indicated in Chart 5. The starting material employed in the experiments here was described as a 40/60 mixture of *Z* and *E* isomers. Table IV shows the relative amounts of products obtained.

In aqueous solution, the reduction of **4** is very slow in the absence of additives and only slightly accelerated in the presence of both CD and DMCD to give, after 4 h, **4A** as the only product (entries 2 and 3). These results are surprisingly different from those obtained for the other substrates investigated; in this case, the effects of the two macrocycles are quite similar and the conversions of citral into products is rather modest, especially if compared to those observed under phase transfer conditions. Under such conditions, in the presence of **8**, after 8 h, citral is completely converted to citronellal **4A** and citronellol **4B** (as racemic mixtures),



4 **4A** **4B**

Chart 5.

TABLE IV. Reduction of Citral **4**

Entry	Time (h)	Additive	**4A** %	**4B** %
1	4	–	1	1
2	4	**6** (CD)	7	–
3	4	**7** (DMCD)	7	–
4	8	**7** (DMCD)[a]	32	–
5	4	**8** (A 336)[a]	66	11
6	8	**8** (A 336)[a]	33	67

[a] In water/toluene.

whereas in the presence of **7** the conversion is only 32%; thus, DMCD is less efficient but more selective than **8**, since, even after 8 h, the alcohol is absent in the reduction mixture (compare entries 4 and 6).

In order to obtain information concerning the mode of inclusion, the i.c.d. spectra of the preformed 1 : 1 complexes of **4** with CD and DMCD were recorded; both spectra (see Figure 1) show a similar negative induced band, suggesting the same mode of insertion of the substrate in the two macrocycles. Inspection of molecular models and previously reported evidence concerning the insertion of esters with a long (6 to 12 carbon atoms) paraffinic chain [6], suggest that **4** should be almost fully inserted into the cavity so that the reacting portion of the substrate, exposed to the solvent, is very little, if any.

3.5. Reduction of (±)-9-methyl-5(10)-octalin-1,6-dione **5**

The reduction of the diketone **5** may follow a rather complicated pattern as shown in Chart 6. In our experiments, products **5C–F** were formed in very small or trace amount only under phase transfer conditions. The yields of the major isolated products, **5A** and **5B** (as mixtures of four and eight stereoisomers, respectively), are reported in Table V.

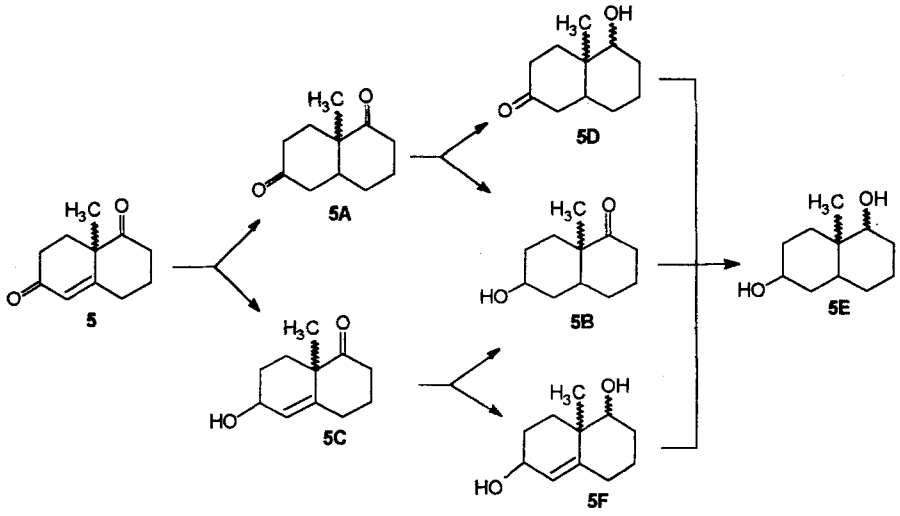


Chart 6.

TABLE V. Reduction of the octalindione **5**

Entry	Time (h)	Additives	**5A** %	**5B** %
1	8	–	–	–
2	1	**6** (CD)	90	10
3	8	**6** (CD)	32	70
4	2	**7** (DMCD)[a]	73	10
5	8	**7** (DMCD)[a]	12	88
6	2	**8** (A 336)[a]	83	8
7	8	**8** (A 336)[a]	15	83

[a] In water/toluene.

Even after 8 h, no reduction products of **5** are detected when the reaction is carried out in the absence of additives. The rate effects are quite impressive in the presence of CD in water and of either **7** or **8** under phase transfer conditions. On the contrary, addition of DMCD does not affect appreciably the rate of reduction with respect to that in bulk water. The results obtained with CD (entries 2 and 3) are of great interest; full conversion of the substrate is achieved after 1 h; the reaction proceeds through two clearly defined steps, the first leading to diketones **5A** and the second one to hydroxyketones **5B** (the latter products were obtained with a ratio of 70/30, similar to that reported for the dithionite reduction in the presence of Adogen [3]). It is here emphasized that, using CD in water or either DMCD or **8** (A 336) in water/toluene, the reduction can be very selective just by modulating the reaction time (see Table V).

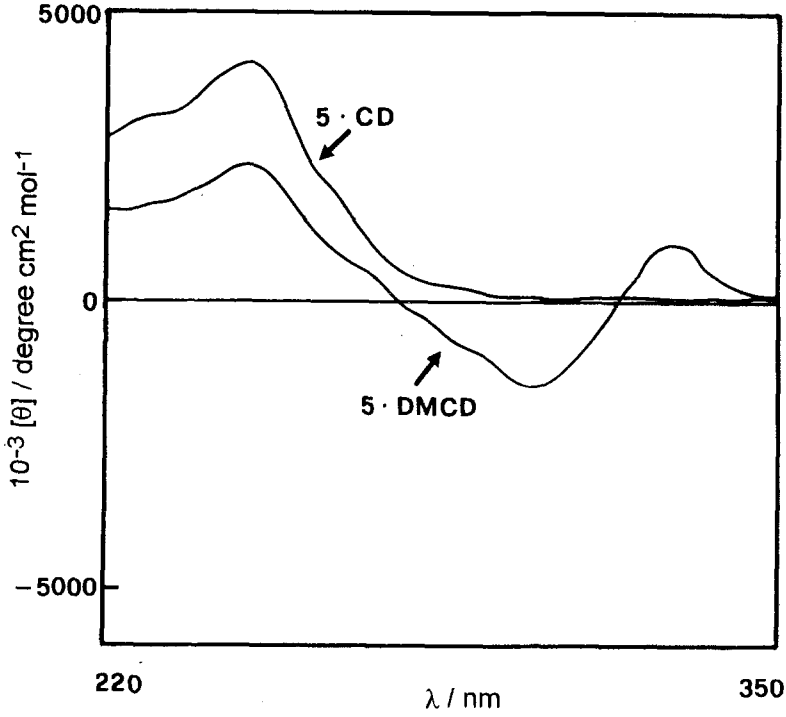
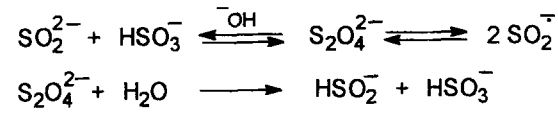


Fig. 2. I.c.d. spectra of complexes of **5** with β-CD and DMβ-CD.

At variance with the other inclusion complexes investigated, the i.c.d. spectra of the 1 : 1 inclusion complexes of **5** with the two macrocycles CD and DMCD are different as illustrated in Figure 2. In the case of **5** · CD there is only one strong and positive band at ca. 245 nm, while in the case of **5** · DMCD the spectrum shows a sequence of bands of alternate sign in the range 220–350 nm, which are difficult to interpret.

4. Discussion

The product distribution observed in the reduction of enones **1–5**, under the conditions explored, depends on a variety of factors: on the structure of the individual substrate, on the presence of the additives and on their nature, on the reaction time and on the homogeneous or double phase conditions. However, a scrutiny of the results reported in Tables I–V indicates some common features that may be summarized as follows: (a) the first step of the reaction always involves the reduction of the conjugated C=C double bond to give the saturated aldehyde or ketone which is, subsequently, transformed into the corresponding saturated alcohol. In some cases, under appropriate conditions (see, for instance, Table III entry 5 and Table IV entries 2–4) the reduction can be stopped after the first step to obtain only



Scheme 1.

the saturated carbonyl compound, although with partial conversion of the enone; (b) in homogeneous aqueous solution, complexation of the enone in CD increases the reduction rate: in some cases (e.g. Table V, entries 1–3) the effect is quite remarkable. On the contrary, complexation with DMCD slows down, in general, the reaction rate or is simply ineffective; (c) under phase transfer conditions, while CD is not a carrier, DMCD is a surprisingly good transfer agent, only slightly less effective but often more selective than Aliquat 336; (d) the effects of complexation on the rate of the reaction and on product distribution are more important for enones **2**, **3** and **5** (as well as for carvone [2]), i.e. for compounds featuring the cyclohexene moiety, than for enones **1** and **4**, whose unsaturations are not a part of a cyclic structure.

The set of results here reported are exceedingly complicated to provide a comprehensive rationale. Therefore, we will confine the discussion to the striking differences highlighted above under points (b) and (c). Any explanation must take into account the following points; (i) the modified macrocycle DMCD is remarkably more hydrophobic than natural CD and the main macroscopic consequence is its much higher solubility in organic media; its cavity may be somehow wrapped up, at least in water, due to the presence of relatively hydrophobic and bulky fences (the methoxy groups in the place of hydroxyls), and, hence, it may be more selective for the inclusion of hydrophobic substances; (ii) the reduction of enones in aqueous solutions in dithionite has been suggested [7] to involve the reaction between the unsatured bonds of the enonic system and the anionic species (either SO_2^- or HSO_2^-, depending on the pH), generated through the equilibria of Scheme 1.

We suggest that, in water, the CD complex, particularly of substances with a rather compact structure, such as enones **2**, **4**, **5**, may also host the ionic species which are responsible for the reductive attack and, hence, speed up the reaction, relative to bulk solvent. The formation of ternary inclusion complexes has been invoked to explain the effect of complexation in a number of reactions, in which one of the reactants is an ionic species [8]. On the other hand, the DMCD complex is probably reluctant to allow the coinsertion of hydrophilic species in its cavity and, therefore, inhibition of the reaction may result.

Alternative explanations appear less tenable. Thus, in the case of CD complexes, the enone may protrude from the cavity in such a way as to allow the unsaturated bonds to interact with the ionic species residing outside the cavity; such interaction should be more difficult in the case of DMCD because of the presence of the

fences on the rims. However, it is rather difficult to explain the very large rate accelerations observed in the case of the CD complexes; in fact, this would imply a consistent accumulation of reducing anionic species at the edge of the CD cavity in the absence of plausible attractive forces.

A good argument, which could explain the difference in reactivity observed, could be provided by different modes of insertion of the enones into the cavity of the two macrocycles; however, this is not supported by the results of the circular dichroism of the inclusion complexes of the enones **2** and **4** with CD and DMCD; in fact, the i.c.d. spectra of such complexes would indicate an axial mode of inclusion for both enones in both type of macrocycles; yet, the reactivity observed is dramatically different.

The idea that the formation of ternary inclusion complexes may be involved in the reduction of enones in the presence of CD could provide a rationale also for the results obtained under phase transfer conditions. Under such conditions, in the presence of native CD, the organic substrate is extracted by toluene from the inclusion complex and resides in the organic phase, separated from the macrocycle and from the ionic species which remain dissolved in water and the reduction, therefore, does not occur. When DMCD is the host, while the substrate is extracted by the organic layer, the macrocycle effectively partitions itself (see Section 2, Experimental) between the two phases: it can move from the aqueous layer, with its cavity containing water and hydrated ionic species, to toluene, where the dissolved enone may react with the reducing species translocated through the outerface and therein released. There is not much room to speculate on whether the reaction occurs in bulk toluene or in the cavity of the DMCD; at any rate the results indicate that the modified cyclodextrin acts as a carrier as effectively as the classical transfer agents such as Aliquat.

Acknowledgements

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