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ORIGINAL ARTICLE

Improved aqueous Cannizzaro reaction in presence of cyclodextrin

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Abstract An aqueous hydroxypropyl-β-cyclodextrin solution has been used to increase the conversion of 4-biphenylcarboxaldehyde into the corresponding alcoholic and carboxylic substrates, by means of a Cannizzaro reaction. The observed enhancement has been ascribed to a partial solubilization of 4-biphenylcarboxaldehyde. In addition, as the main part of the organic substrates still remains insoluble, synthesized products are easily recovered by filtration. As a consequence, the basic cyclodextrin solution might also be reused for a new synthetic cycle, without significant loss of conversion. Aqueous solid–liquid biphasic reaction in presence of cyclodextrins thus seems to be a promising tool in the green chemistry field.

Keywords Cyclodextrin · Phase transfer agent · Solid–liquid reaction · Cannizzaro Reaction

Abbreviation
HPBCD Hydroxypropyl-β-cyclodextrin

Introduction

One of the main limitations in carrying organic reactions in water is the limited solubility of most organic reactant. As cyclodextrins generally improve aqueous solubility [1–3], these macrocycles may be used to increase feasibility of organic reaction in presence of water. For instance, this concept has been widely applied in liquid–liquid biphasic catalysis [4–9]. Cyclodextrins then act as a phase transfer agent, between the two liquid phases. As cyclodextrins could also act as a solid–liquid phase transfer agent, we have decided to demonstrate in this study that they could be used to extend known reactivity in pure water to solid hydrophobic substrates. The concept of solid–liquid reactions assisted by cyclodextrins is described in Fig. 1.

If an adequate amount of cyclodextrin is used, only a part of the reactant might be solubilized. Thus, while an enhanced reactivity could be observed as a consequence of a greater reactant aqueous concentration, most of the organic compound still remains in solid state. This means that organic reactions might be carried out until completion, while purification may be then realized by simple filtrations. As a consequence, the desired product could be separated from the aqueous cyclodextrin solution, which could be then reused for a new cycle of conversion.

In order to validate such a concept, we have applied this principle to a Cannizzaro reaction, using insoluble 4-biphenylcarboxaldehyde in presence of hydroxypropyl-β-cyclodextrin (HPBCD). If Cannizzaro reactions have been widely used in water, they have been restricted to low molecular weight organic compounds [10–13], or achieved in presence of cosolvent [14, 15], under supercritical conditions [16] or under microwave irradiation [17]. The Cannizzaro conversion of large hydrophobic compounds in "pure" water is thus a challenging task. Within this scope, the present work presents the influence of aqueous HPBCD solution on the Cannizzaro conversion of 4-biphenylcarboxaldehyde, but also the characterization of the corresponding complex by molecular modeling and solubility

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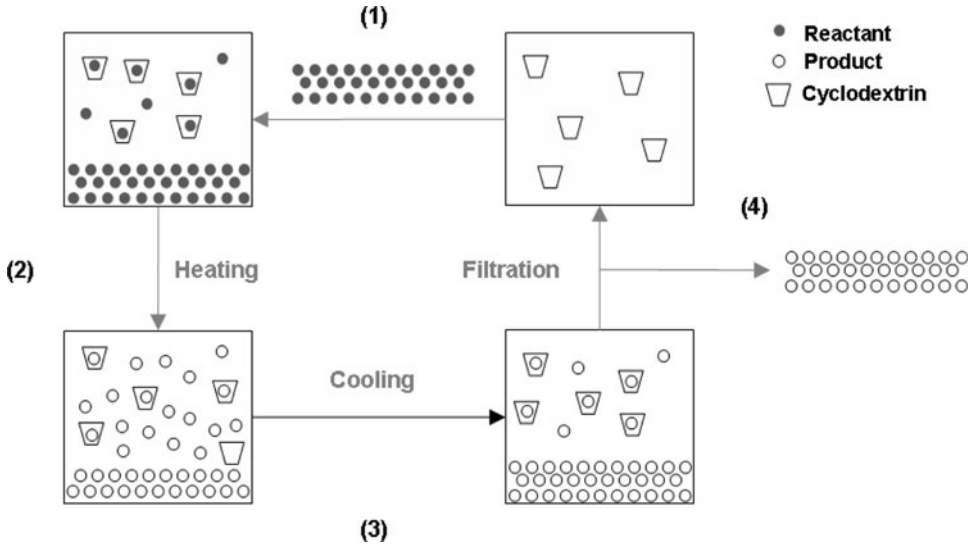

Fig. 1 Recyclable solid/liquid reaction assisted by cyclodextrins

studies, as well as the recyclability of the basic cyclodextrin solution.

Experimental details

Materials

All chemicals were purchased from Aldrich, except HPBCD (mean molecular weight equal to 1500 g/mol) which was kindly donated from Roquette Frères (Lestrem, France). ^{1}H (250 MHz) and ^{13}C (60 MHz) NMR spectra were recorded with a Brüker ASPECT 3000 spectrometer, in DMSO-d_6. UV–Vis spectrometry was performed with a UV–Vis PERKIN ELMER Lambda 2S spectrometer (temperature kept constant to 25 °C by a thermostated bath).

Synthesis

200 mg of 4-biphenylcarboxaldehyde were added to 30 mL of a 20% potassium hydroxide aqueous solution, in absence or in presence of 200 mg HPBCD. The suspension was heated at 50 °C during 24 h. The reaction mixture was then filtered, potassium hydroxide and HPBCD being inside filtrate (which may be reused for a new conversion) while products being precipitated. Products were then washed with cold 1 M HCl solution in order to convert 4-biphenylcarboxylate into its acidic form. 4-Biphenylmethanol and 4-biphenylcarboxylic acid are then submitted to separation by column chromatography (silica gel, ethyl acetate 100%), and then dried. The products were commercially available and the structures were confirmed by comparison of their ^{1}H and ^{13}C NMR spectra.

Solubility study

10 mL of HPBCD solutions (prepared by adequate amounts of solid HPBCD added to pure distilled water) were added at various concentrations: 0, 0.8, 1.7, 3.3 and 6.7 mM. 4-Biphenylcarboxaldehyde absorption in CD solution was then analyzed by UV–Vis spectrometer, and was used to evaluate the apparent solubility of 4-biphenylcarboxaldehyde, which is defined as the amount of 4-biphenylcarboxaldehyde in solution in presence of HPBCD. For each HPBCD concentration, three runs were realized. The absorbance was used to evaluate soluble 4-biphenylcarboxaldehyde concentrations, which were then plotted against HPBCD concentrations. The straight lines thus obtained allowed the determination of formation constant K, by means of their corresponding slopes S and of 4-biphenylcarboxaldehyde solubility [4-biphenylcarboxaldehyde]$_0$ in absence of HPBCD [2]:

$$K = \frac{S}{[\text{4-biphenylcarboxaldehyde}]_0 * (1 - S)}$$

Molecular modeling

Simulations were realized by means of Macromodel [18] with MMFF force field and GB/SA simulation of water [19]. A symmetric CD structure was used to construct HPBCD. HPBCD was simulated by an isomer which was hydroxypropylated two times on primary hydroxyls and four times on secondary hydroxyls. This structure only represents one of the multiple products of the HPBCD mixture, but it should be representative of the steric contribution of hydroxypropylation. Hydroxypropyl arms were submitted to a Monte Carlo conformational search prior to host–guest docking. The docking of 4-biphenylcarboxaldehyde inside HPBCD

was realized by means of Monte Carlo searches, with generation of 10000 conformations (Polak-Ribiere Conjugate Gradient minimization, convergence fixed to 0.05 kJ/Å mol). 4-Biphenylcarboxaldehyde was freely modified while HPBCD was kept rigid. The most stable conformation for each inclusion compound was then completely relaxed (convergence fixed to 0.05 kJ/Å mol).

Results and discussion

Heating (50 °C) of a 4-biphenylcarboxaldehyde suspension in an aqueous potassium hydroxide solution leads to the formation of the corresponding alcoholic and carboxylated substrates, with conversion yields depending on the absence or presence of HPBCD (Fig. 2).

While only 30% of the initial reactant is converted in 24 h in absence of cyclodextrin, the organic reaction takes place in a quantitative way (99%) in presence of HPBCD. The solution is then easily filtered, leading to the recovery of 90% of synthesized products. Moreover, no cyclodextrin is observed in the precipitated products after filtration, as evidenced by ^{1}H NMR. It has also to be mentioned that the use of smaller concentrations of HPBCD or potassium hydroxide leads to weaker reaction yields. On the contrary, high reaction yields are still obtained when increasing concentrations of these reactants, but it induces a decrease of the recovery yields. This is especially true for high potassium hydroxide quantities, which lead to an increase of viscosity and which prevent efficient filtrations. The proposed experimental conditions thus represent optimized ones.

When a substrate reactivity is enhanced in presence of cyclodextrins, it is generally ascribed to the formation of an inclusion compound between the two species. As a consequence, we have studied the steric complementarity between 4-biphenylcarboxaldehyde and HPBCD by means of molecular modeling. 4-Biphenylcarboxaldehyde has been submitted to Monte Carlo searches (MMFF force field), with an implicit representation of water (GB/SA). The most stable conformations which have been simulated are illustrated in Fig. 3.

One can observe that the whole 4-biphenylcarboxaldehyde structure might be encapsulated in HPBCD cavity, with, as a consequence, an important stabilization in term of enthalpy (up to 16.7 kcal/mol). Even if the well known enthalpy/entropy compensation is not evaluated in these simulations, such energetic values of stabilization suggest that HPBCD cavity is well suited to 4-biphenylcarboxaldehyde, and that a stable complex should be observed between the two species. More specifically, the aldehyde part of 4-biphenylcarboxaldehyde might be exposed to both primary and secondary rims of cyclodextrin. Even if the secondary rim is more open and gives rise to a better exposition of aldehyde to external hydroxide, the accessibility of such aldehyde also appears to be sufficient when it is exposed to primary rim. Thus, we may reasonably think that Cannizzaro reactions might occur not only for the free soluble part of 4-biphenylcarboxaldehyde but also inside the inclusion compound, whatever conformation is considered.

As a consequence, it is not surprising that an enhanced reactivity is observed in presence of cyclodextrins, if, in addition, the formation of an inclusion complex between the insoluble 4-biphenylcarboxaldehyde and the highly soluble HPBCD leads to a greater concentration of 4-biphenylcarboxaldehyde in solution. We have thus tried to demonstrate the influence of cyclodextrin on the aqueous 4-biphenylcarboxaldehyde solubility, by means of UV–Vis spectroscopic measurements. A linear relationship between the apparent solubility of 4-biphenylcarboxaldehyde versus CD concentrations (from 0 to 6.7 mM) is indeed observed with a high correlation factor, as seen in a typical set of results (Fig. 4).

The 4-biphenylcarboxaldehyde solubility is rapidly increasing with HPBCD concentration, 1 mM of cyclodextrin being sufficient to solubilize 0.5 mM of 4-biphenylcarboxaldehyde. A 28 times improved solubility is even obtained for a 7 mM HPBCD solution (4-biphenylcarboxaldehyde solubility then equal to 3 mM). Moreover, the fact that a straight line is obtained allows the evaluation of the binding stability for HPBCD/4-biphenylcarboxaldehyde inclusion compound. A formation constant of $7800 \pm 1200\ M^{-1}$ is calculated, thus confirming a good complementarity between the two species, as previously underlined by our modeling study.

These solubility and stability results highlight the experimental conditions required by the concept of solid–liquid reactions assisted by cyclodextrins. Indeed, when

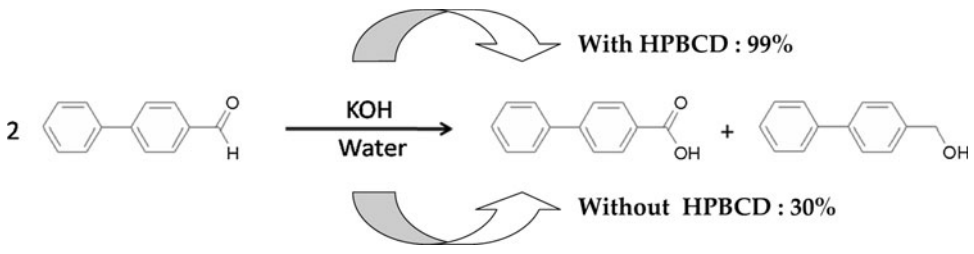

Fig. 2 Cannizzaro conversion of 4-biphenylcarboxaldehyde into 4-biphenylmethanol and 4-biphenylcarboxylic acid

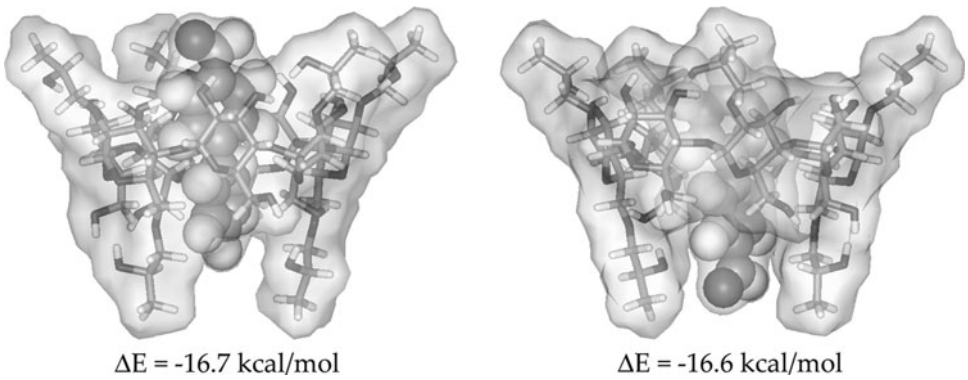

Fig. 3 Most stable structures of HPBCD/4-biphenylcarboxaldehyde and energetic stabilization, as simulated by Monte Carlo searches (MMFF-GB/SA)

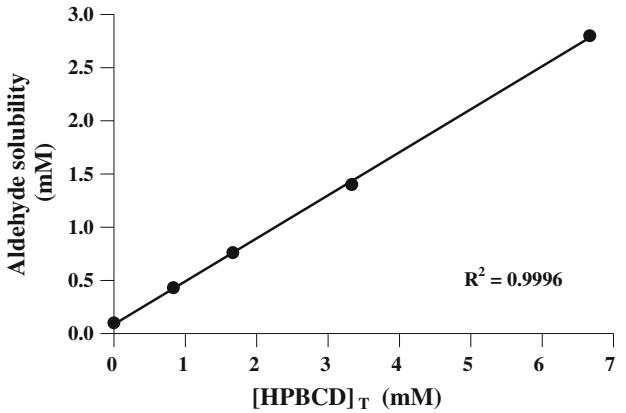

Fig. 4 4-Biphenylcarboxaldehyde solubility in function of HPBCD concentration

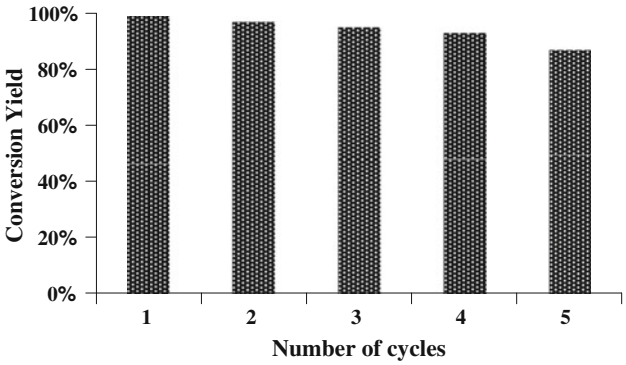

Fig. 5 Conversion yields for five consecutive cycles of Cannizzaro reaction on 4-biphenylcarboxaldehyde in presence of HPBCD

1.10 mmol (200 mg) of 4-biphenylcarboxaldehyde is mixed with 4.40 mmol (200 mg) of HPBCD, only 0.05 mmol of complex is formed, leading to the solubilization of only 0.05 mmol of 4-biphenylcarboxaldehyde. Nevertheless, it represents a quantity which is 16 times superior to 4-biphenylcarboxaldehyde solubility in absence of cyclodextrin, and it explains why a significant conversion enhancement is observed in presence of HPBCD. It also accounts for the good recovery of the synthesized products by a simple filtration, since 95% of 4-biphenylcarboxaldehyde is still in solid form, while HBCD is exclusively in solution. The fact that greater cyclodextrin concentrations might induce weaker recovery yields is also explained, since a greater 4-biphenylcarboxaldehyde quantity is then maintained in aqueous phase when reaction mixture is filtered. As reaction yield is already close to 100% when 4.40 mmol of HPBCD is used, it is thus unfavorable to increase the cyclodextrin amount.

Since desired products and phase transfer agents (HPBCD) might be easily separated from each other, recyclability of the HPBCD/potassium hydroxide aqueous solution could also be allowed. As a consequence, five consecutive Cannizzaro cycles have been achieved with the same initial solution, to which 200 mg of 4-biphenylcarboxaldehyde were simply added after each cycle. As could be seen from Fig. 5, these consecutive reactions take place without significant loss of conversion (with products recovery being stable and close to 90%).

A slight diminution is observed however, but it might be ascribed to the natural consumption of reactant, since 1 equivalent of potassium hydroxide is needed for the formation of alcoholic and carboxylated substrates. Moreover, a slight quantity of solution is lost upon each filtration, thus decreasing the presence of both HPBCD and potassium hydroxide. This could be easily compensated by adding the little corresponding losses after each cycle.

In summary, this study has demonstrated that an aqueous HPBCD/potassium hydroxide could be used to enhance the Cannizzaro conversion of 4-biphenylcarboxaldehyde into the corresponding alcoholic and carboxylic substrates, in a quantitative and recyclable way.

Conclusions

In this work, the concept of solid–liquid reactions assisted by cyclodextrins has been illustrated in the case of a Cannizzaro reaction. It could be extended to any typical reactivity which takes place in water, for any solid substrate which would be insufficiently hydrosoluble and

which could also form inclusion compounds with cyclodextrins. Depending on the substrate solubility in absence and in presence of cyclodextrin, the quantity of cyclodextrin has simply to be adjusted to enhance the substrate concentration, in a significant but not in a quantitative way. As a great number of organic compounds are not only hydrophobic but also well recognized by cyclodextrins, the concept of solid–liquid reactions assisted by cyclodextrins could be widely applied. As a consequence, this study opens the way to new applications of cyclodextrins in the green chemistry field.

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