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Particle size effect in the mechanically assisted synthesis of β-cyclodextrin mesitylene sulfonate

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Abstract

Mechanically assisted synthesis of organic compounds has recently focused considerable attention as it may be unique in features to selectively orient the reaction pathway. In the continuation of our work on the synthesis of modified cyclodextrins (CDs) via mechanochemical activation, we sought to discriminate the contribution of supramolecular effects and grinding during the course of a reaction in the solid state. As such, we recently investigated the influence of the particles size of β-CD in the synthesis of β-CD mesitylene sulfonate (β-CDMts) in the solid state using a vibrating ball-mill. We were particularly interested in the role of the particles size on the kinetics of the reaction. In this study, we show that grinding β-CD reduces the particles size over time down to a limit of 167 nm. The granulometric composition remains rather

invariant for grinding times over 1 h. Each type of β-CD particles reacted with mesitylene sulfonic chloride (MtsCl) to produce β-CDMts. Contrary to what could be intuitively anticipated, smaller particles did not lead to the highest conversions. The impact of grinding over the conversions was limited. Interestingly, the proportion of β-CDMts mono-substituted on the primary face significantly increased over time when the reaction was carried out in the presence of KOH as a base. The data series were confronted with kinetics models to get clues on the way the reactions proceeded. The diversity of possible models suggests that multiple mechanochemical processes can account for the syntheses of β-CDMts in the solid state. Throughout this study, we found that the reactivity depends more upon diffusion phenomena in the crystalline parts of the material than upon the increase in the surface area of the CD particles resulting from grinding.

Keywords

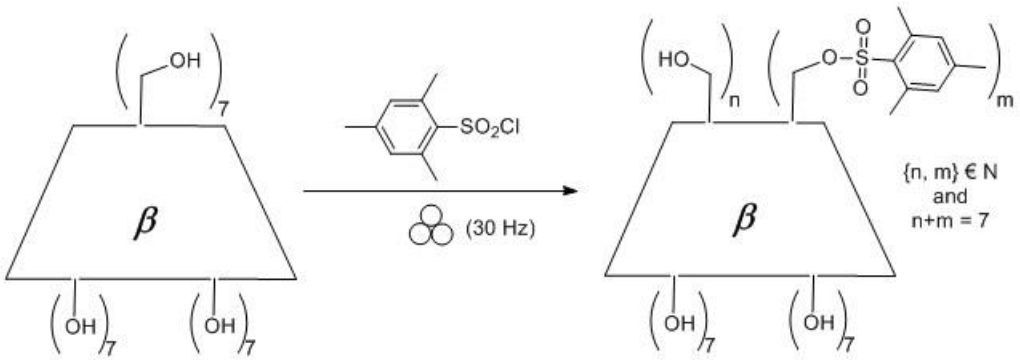
mechanosynthesis; beta-cyclodextrin; grinding; reactivity; chemoselectivity

Introduction

Mechanically assisted synthesis of organic compounds offers several advantages over organic reactions performed in solution. Upon grinding, both the reactivity and the reaction selectivity are usually improved [1-6], resulting in a reduced reaction time and a limited number of purification steps. We especially focused our attention on the utilization of cyclodextrins (CDs), which are cyclic α-D-glucopyranoside-based saccharides. CDs feature the advantages of adjustable cavity size and broad synthetic diversity. The most commonly used CDs are α-CD, β-CD and γ-CD, that consist of 6,

7 and 8 α-D-glucopyranoside units, respectively. CDs are recognized as effective excipients in the formulation of numerous drugs [7-10]. Upon grinding, CDs form inclusion complexes with drugs in the solid state, resulting in significantly faster dissolution rate and greater bioavailability enhancement [11-13]. In our previous studies, CDs act either as reactants [14,15] or as additives [16,17], and develop supramolecular interactions with the other partners of the reaction. We showed that the formation of CD/substrate supramolecular complexes favor the dispersion of the reactants throughout the solid mixture under ball-milling conditions. Weak association of bulky substrates and/or their corresponding products with the CD cavities under ball-milling conditions improved the mobility of the partners in the solid state. The reaction reactivity and selectivities were then greatly improved. However, it is not clear whether the increase in reactivity is only a consequence of the formation of inclusion complexes, or whether the grinding process is also involved, and if so to which extent. Accordingly, quantification of the grinding contribution in the reactivity is lacking at this stage. Indeed, grinding provokes comminution of the reactants and may greatly alter the physical properties of the materials with potential effects on the reactivity. To assess the contribution of both grinding and supramolecular effects over the reactivity, we got rid of supramolecular effects to only focus on the influence of grinding the CDs prior the mechanically assisted reaction on kinetics. In this context, we considered the synthesis of mono- and poly-β-CD mesitylene sulfonate (β-CDMts) from β-CD and mesitylene sulfonic chloride (MtsCl) as a model reaction. MtsCl was found to be a non-interactive guest towards the CD host [18], meaning that no inclusion compounds could be formed during the course of the reaction. Previous works dealing with this reaction showed that β-CDMts featuring a defined number of mesitylenesulfonate groups could be obtained selectively in solution after tedious work-up [19-21]. The current

investigations were aimed at fabricating β-CDMts samples through mechanochemical activation from mixtures of MtsCl and β-CD featuring different particles sizes (Scheme 1). The following study shed light on the role of the grain size of β-CD constituting the reaction mixture over the reactivity of the synthesis of β-CDMts under ball-milling conditions. Additionally, in the presence of a base such as KOH, we show that the chemoselectivity of the reaction is significantly altered in favor of the β-CD derivative mono-substituted on the primary face, thus highlighting the advantages of such mechanically assisted synthesis.



Scheme 1: Mechanically assisted synthesis of mono- and poly-β-CD mesitylene sulfonate (β-CDMts).

Results and Discussion

Analysis of ground CDs

Scanning electron microscopy (SEM)

SEM enables particle size evolution upon grinding to be monitored. SEM images shows the surface topography changes of polycrystalline β-CD for six different milling times (Figure 1).

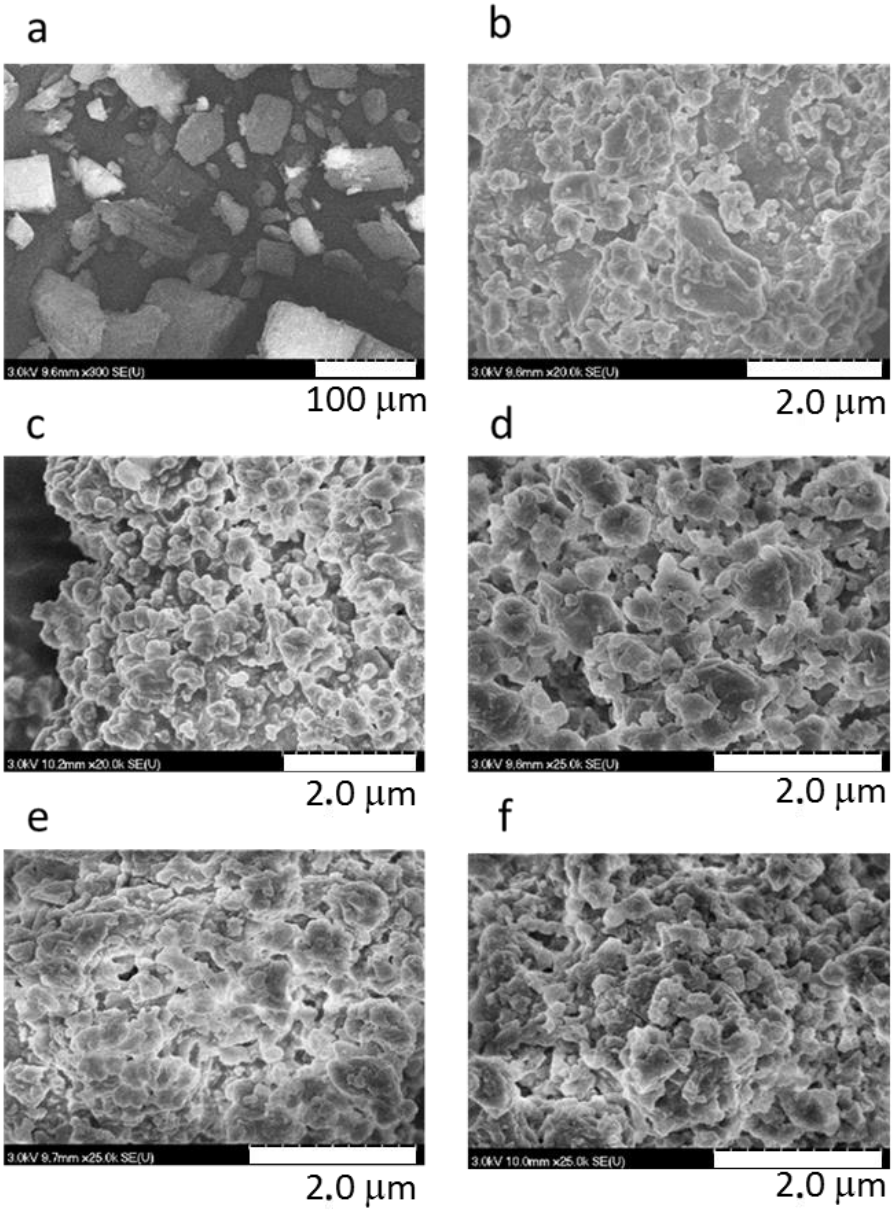


Figure 1: SEM images of β-CD particles a) before grinding, and ground for b) 5 min, c) 10 min, d) 29 min, e) 85 min, and f) 297 min.

The powder particles experience comminution and decrease in size. After grinding for 10 min, β-CD displays microsized particles as shown in Figure 1c. Longer grinding times provide small particles below 300 nm in diameter (Figures 1d and 1e). Their spherical morphology could be deduced from the Solidicity program of the Image-J software. Further grinding up to 297 min did not change either the morphology or the

size of the β-CD particles (Figure 1f). From the SEM images and the Image-J software, we also calculated the granulometric composition of the β-CD particles against the grinding time (Figure 2). While a rapid decrease in size is observed over the first 10 min, a slight variation on the particle size is noticed when the grinding of β-CD was left to occur over longer times, suggesting that shear, friction and collision effects do not anymore affect the β-CD particles size and morphology over time. In fact, crystal breaking reduces the particles size reduction up to some critical threshold, as a result of the equilibrium between comminution and aggregation.

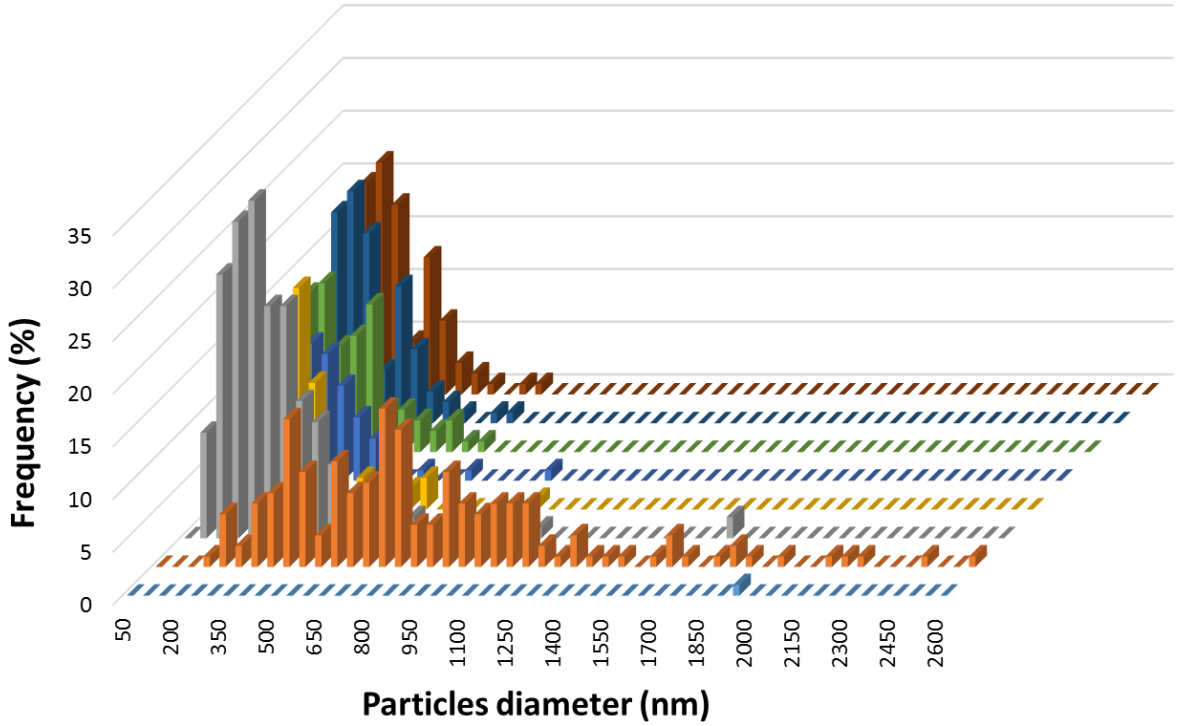


Figure 2: Granulometric composition of β-CD particles against time after grinding at 30 Hz. 0 min, 1 min, 5 min, 10 min, 15 min, 29 min, 85 min, 297 min.

From the SEM images and using the ImageJ software, we then measured the size of the β-CD particles. The calculated Feret mean diameter (mean value of the Feret diameters over all orientations, i.e. 0-180°) are gathered in Table 1.

Table 1: Variation of the physical properties of β-CD particles against grinding time.

Grinding time (min)	0	1	5	10	29	85	297
Feret mean diameter (nm)	37870	839	308	303	278	235	235
SSA ($cm^2.g^{-1}$)	0.28	3.61	7.57	12.72	16.48	19.7	22.66
Powder density ($g.cm^3$)	1.57	1.91	1.90	1.90	1.69	1.60	1.59
Particles size (nm) (BET)	13649	870	314	248	215	190	167

BET analysis

The particles size was also confirmed from the Bruanuer-Emmer-Teller *(BET)* surface adsorption method. The obtained values are in good agreement with those obtained from the exploitation of the SEM images (Table 1). The specific surface area (SSA) of the β-CD samples ground over various periods of time was also extracted from the BET analysis (Table 1). Increase in SSA is logically observed upon grinding because of the reduction of the β-CD particles size.

XRD analysis

X-ray diffraction data give additional evidence of the crystallinity variation of the β-CD particles upon grinding. Figure 3 shows a series of X-ray powder diffraction patterns recorded at various grinding times, and establish the extent of the amorphization of the reaction mixture during mechanochemical milling.

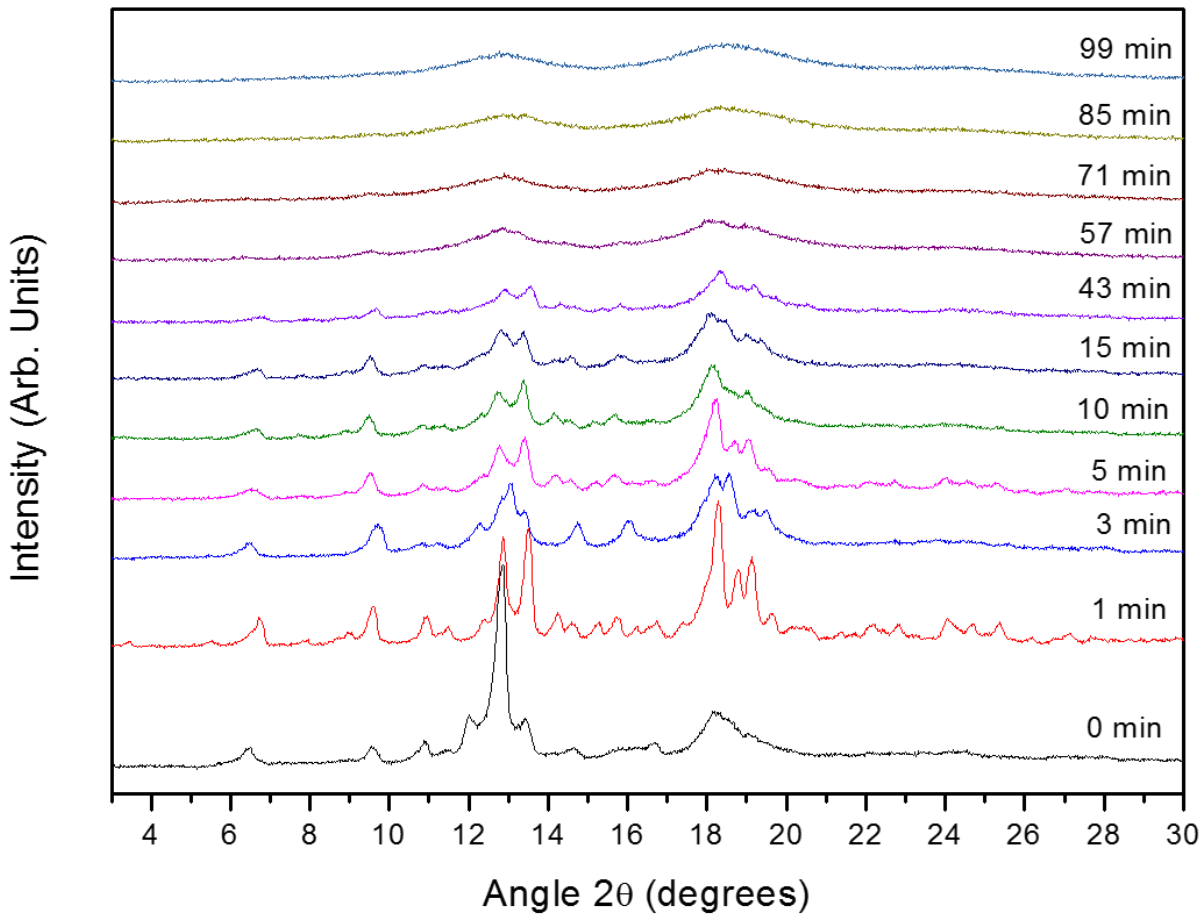


Figure 3: XRD patterns of β-CD powder at different grinding times.

Peaks corresponding to pure β-CD crystals decrease over time. Clearly, the polycrystalline β-CD powder amorphizes over time. Amorphization is usually described as a process starting on a thin surface layer and then propagating into the bulk [22], which impedes the structure and property characterization of the material. However, a significant fraction of residual crystalline domains still exists even after 1 h grinding. This is in line with the previous results showing the absence of variation of the particles size when increasing the grinding time. Over time, grinding do not further alter the particles and no more cracks in crystal grains can take place.

Syntheses of β-CDMS

Once the β-CD particles were characterized upon grinding over various grinding times, we carried out the synthesis of β-CDMts. Ground β-CD and MtsCl were poured in the jars and shaken at 30 Hz. The conversion was plotted against the grinding time. The first set of experiment compares conversions obtained without preliminary grinding β-CD and with ground β-CD particles (average size ~ 235 nm) (Figure 4).

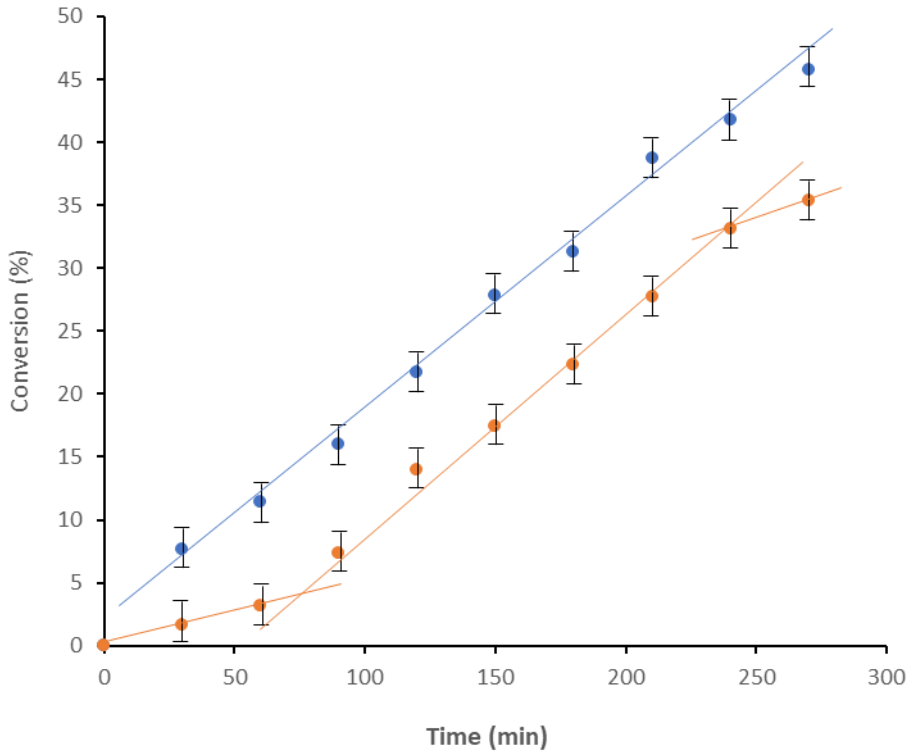


Figure 4: Compared conversions of β-CD in the synthesis of β-CDMts without grinding β-CD (●) and with ground β-CD (~235 nm) (●).

The data series related to ground β-CD shows sigmoidal kinetics, as already observed for mechanically assisted organic reactions described in the literature [23]. The induction period with ground β-CD is approximately 1 h. Conversely, the data series related to the synthesis performed without grinding β-CD shows a linear variation. Note that, without grinding, reaction times beyond 270 min do not improve significantly the

conversion as a plateau at ~55% conversion is reached over time. Surprisingly, contrary to what is commonly observed in the literature for solid-state addition reactions [24,25], it appears that a reduction of the β-CD particle size slightly decreases the percent conversion. However, the counterintuitive effect is rather limited, suggesting that grinding β-CD prior the reaction does not strongly modify the way reactants interact with each other to produce β-CDMts.

The results were also analyzed in terms of relative proportions of mono- and poly-substituted compounds. The mono/poly-substituted β-CDMts ratio strongly varies upon grinding over time, as illustrated in Figure 5.

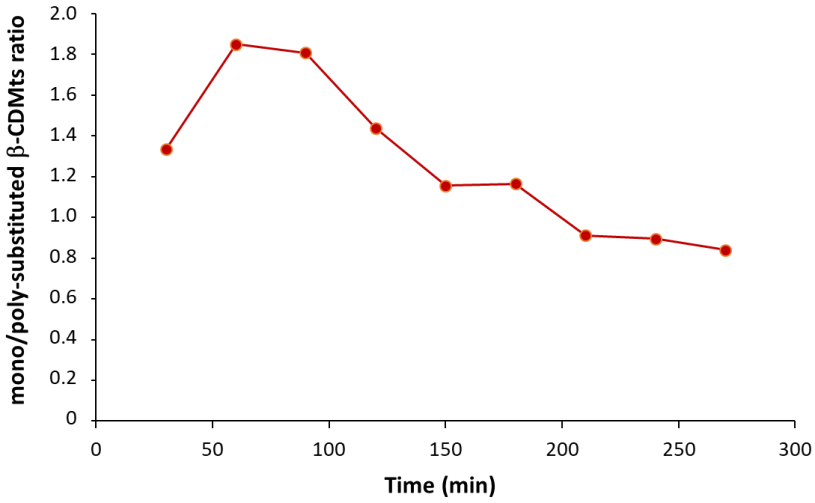


Figure 5: Variation of the mono/poly-substituted β-CDMts ratio with time in the absence of a base.

The ratio calculated at 30 min is impaired with uncertainty due to the weak conversions within the margin of error (<5%). For other reaction times, the mono/poly-substituted β-CDMts ratios regularly and logically decrease over time, as more poly-substituted derivatives are produced. Note that, despite milling was periodically interrupted, no by-

products were formed along with the expected mono- and poly-substituted β-CD derivatives, contrary to what is sometimes reported in the literature [26-27].

A second set of experiments was carried out in the presence of KOH as a base. Interestingly, the reaction is much faster as the plateau is reached after ~150 min (vs ~300 min without base) (Figure 6). Here again, a slight decrease in the conversion is observed if β-CD is ground prior the reaction, but to a limited extent. Hence, the reactivity of the studied solid-solid reaction cannot be described only in terms of interfacial area of contact between the reactants.

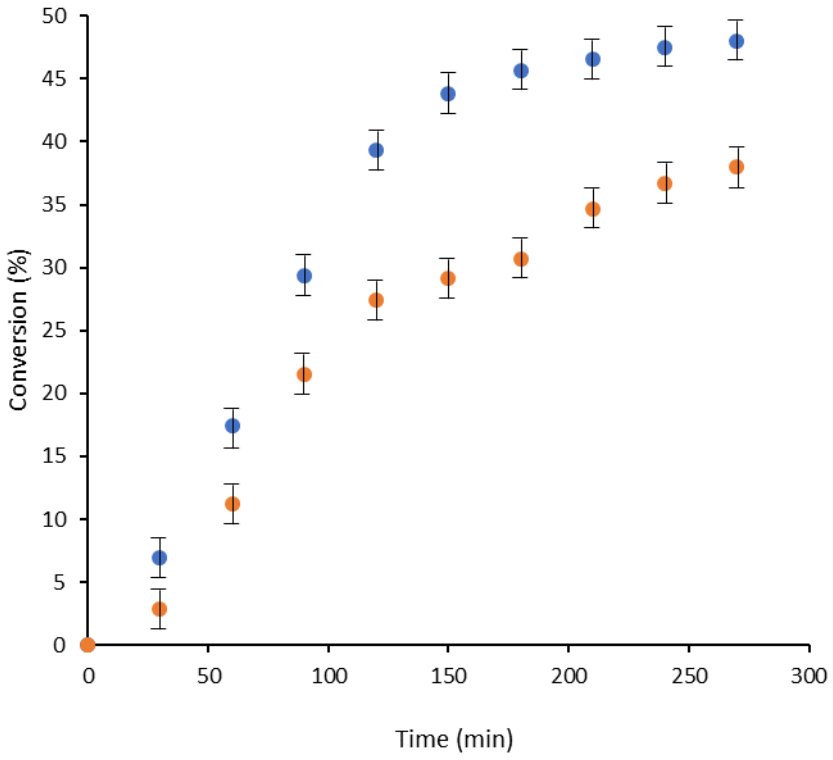


Figure 6: Compared conversions of β-CD in the synthesis of β-CDMts in the presence of KOH (stoichiometric proportion with respect to β-CD) without grinding β-CD (●) and with ground β-CD (~235 nm) (●).

Conversely, in terms of relative proportions of mono- and poly-substituted compounds, the situation is strongly different whether the reaction is carried out in the absence or in the presence of a base. Indeed, in the presence of KOH (and excluding the ratio at 30 min for reasons commented upon above), the proportion of mono-substituted β-CDMts over poly-substituted β-CDMts derivatives increases over time, as depicted in Figure 7. This probably results from the homogeneous diffusion of KOH within the solid mixture that facilitates the deprotonation of a large number of β-CDs rather than only few of them. While deprotonation/protonation equilibriums preferentially take place at the 2- and 6-positions of the β-CD [28], the alcoxide located on the primary face at the 6-position is more inclined than the alcoxides of the secondary face at the 2-position to react with the bulky mesitylenesulfonate group. Accordingly, the formation of mono-substituted β-CDMts is greatly favored. The mechanically assisted synthesis of β-CDMts from β-CD and MtsCl in the presence of KOH thus appears to be a rather selective process, and has a considerable advantage over similar syntheses carried out in solution [19].

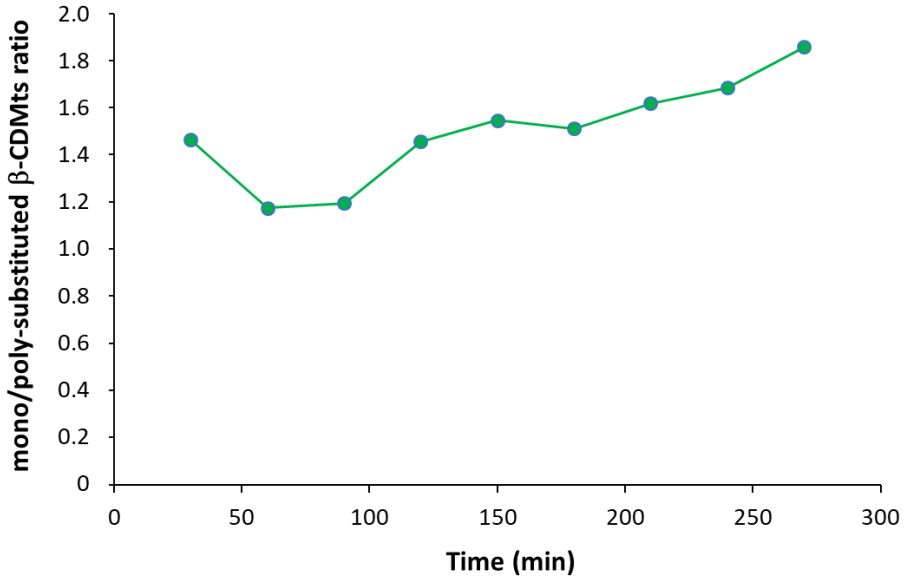


Figure 7: Variation of the mono/poly-substituted β-CDMts ratio with time in the presence of KOH (stoichiometric proportion with respect to β-CD).

Solid-state kinetic models

We then tried to define a kinetic model for the synthesis of β-CDMts. The commonly used solid-state kinetics models considered in this study were described in a paper by Khawam and Flanagan, and made use of an adapted version of the conversion fraction α, that we defined as the ratio of the conversion at time *t* to the final conversion (Table S1) [29]. Based on the highest value of determination coefficient, R^2, we found that no general trend emerges from these calculations of α, whether the CD was ground or not (SI, Figure S1). The presence of KOH did not significantly change the results (SI, Figure S2). The diversity of cases is even more pronounced for α than for conversions. Nevertheless, once the α values were calculated, we tried to fit the data series with kinetics models considering the highest R^2 values. In the syntheses of β-CDMts performed without grinding β-CD or with ground β-CD, the best fit is obtained for B1, the Prout-Tompkins nucleation model (SI, Table S2). In the presence of KOH, the best fit is for F1, a reaction-order model (SI, Table S3). Accordingly, it appears that different models sound appropriate to picture the reaction kinetics, meaning that the process probably results from various contributions, including nucleation, geometrical contraction, diffusion and reaction-order models. However, one should be aware of the highly speculative nature of such interpretations because of the multiple processes (amorphization, particle comminution, product removal to form fresh reactant surface) operating during ball-milling.

Conclusion

While the nature of the grinding processes is still not entirely clear for the synthesis of β-CDMts, the magnitude of their contribution can nevertheless be assigned in a consistent way through the quantitative analysis depicted in this study. In view of the results, grinding and amorphization of CDs are not systematically favorable to reactivity. Moreover, grinding CD prior the reaction appears to have a limited effect on the activation. Hence, the reaction rate is not directly proportional to the aggregate total active area of contact between reactants. However, in the presence of KOH as a base, the mechanically assisted reaction is revealed under a new light as grinding results in a more selective synthesis of mono-substituted β-CDMts, that renders the advantage of mechanosynthesis over synthesis carried in solution.

The synthesis of β-CDMts were not amenable to facile and systematic determination of a unique solid-state kinetics model. Indeed, we fitted the conversion fraction dependence to seventeen solid-state reaction models. The obtained results rather converge to the existence of multiple mechanochemical processes during the course of the reaction. This observation highlights the contribution of the supramolecular effects described in our previous studies. It becomes clear that, for reactions taking place over very short times, we were dealing with crystalline CDs for which the diffusion of the substrate was favored throughout the material by means of supramolecular effects (diffusion through channels). Consequently, the reactivity is much more linked to diffusion phenomena in the crystalline parts of the material than to the increase in the surface area of the CD particles resulting from grinding.

Experimental

Materials

β-CD (98%) was purchased from Roquette Frères (Lestrem, France). Mesitylene sulfonic chloride (MtsCl, 99%) and potassium hydroxide (90%) were purchased from Sigma-Aldrich. All chemicals were used without further purification.

Preparation of β-CD samples

Grinding of β-CD was performed in a laboratory-scale ball-mill (Retsch MM400) equipped with 10 mL zirconia grinding jars containing one zirconia ball (9 mm ⌀). The grinding jars are subjected to radial oscillations in a horizontal position. β-CD in the solid state was poured in the grinding jars, which were subsequently shaken at room temperature at a 30 Hz ball-milling frequency (frequency of the rocking back-and-forth motion conducted by the reaction jar holder). In a stepwise approach, milling is periodically interrupted every 5 min to the jars were opened after a given time and the powder was collected and analyzed. The reaction mixture was characterized by ^{1}H NMR.

X-ray powder diffraction

X-Ray Diffraction (XRD) measurements were performed using a Rigaku ULTIMA IV diffractometer equipped with Cu anticathode (λK_α = 1.5418 Å), Soller slits to limit the divergence of X-ray beam and a nickel foil filter attenuates the Cu K_β line. XRD patterns were recorded in the range of 3°-50° (scan speed of 0.4°/min) using the Bragg-Brentano configuration.

Scanning electron microscopy

Scanning electron microscopy (SEM) images were recorded on a SEM JEOL JSM-7800F LV at 3.0 kV. The powder was deposited on a carbon coated copper grid.

Particles size distributions have been determined from the measurement of ca. 225 particles found in arbitrarily chosen area of the images using ImageJ software (Ver. 1.4.3.67) [30]. After calibrating from the scale of the SEM images, the software provides the Feret diameter.

BET (adsorption de N_2)

N_2 sorption isotherms were collected at -196 °C using an adsorption analyzer Micromeritics Tristar II 3020. Prior to analysis, 80 mg samples were outgassed at 100 °C overnight under vacuum. The specific area were computed using the Brunauer-Emmett-Teller (BET) equation over a range of relative pressure (P/P^0) from 0.001 to 1, while the pore size distribution was measured from the desorption branch using the NLDFT (nonlocal density functional theory) model assuming a cylindrical pore structure. The average pore size is determined by the Dubinin–Radushkevich (DR) plot of the N_2 desorption isotherm. The relative microporosity percentage is defined as the ratio of the micropore volume to the total pore volume. The relative errors were estimated to be the following: S_{BET}, 5%; pore volume (pv) (DFT), 5%; pore size (ps) (DFT), 20%. Isotherms were measured on a Quantachrome® ASiQwin™ instrument at 0 and 21 °C. The temperature was held constant throughout the experiments.

NMR

^1H NMR spectra were recorded on a 300 MHz Bruker Avance III HD spectrometer using D_2O (99.92% isotopic purity, Eurisotop) as a solvent.

Kinetics

The synthesis of β-CDMts from β-CD and MtsCl was selected as an example of a solid-solid addition reaction with a 1:1 stoichiometry. β-CD and MtsCl in the solid state (stoichiometric proportions) were poured in the grinding jars, which were subsequently shaken at room temperature at a 30 Hz ball-milling frequency (see SI). The jars were regularly opened and the compact was triturated with a spatula to recover the powdery solid. Samples were then collected, dissolved in DMSO-d6, and analyzed by ^{1}H NMR to determine the conversion and selectivity (by comparison with reference spectra). Each reaction was repeated twice to ensure the repeatability of the results. Each data point is the average of the two obtained values.

Supporting Information

Supporting Information File 1:

File Name: BJOC Hapiot SI

File Format: Word

Acknowledgements

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