Chitosan hydrogel: A green and recyclable biopolymer catalyst for aldol and Knoevenagel reactions

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Chitosan hydrogel is efficiently utilized as an organocatalyst for aldol and Knoevenagel reactions, providing the products in high yields with a high chemoselectivity under biphasic conditions. The catalyst was recovered by simple filtration and reused several times without significant loss of activity.

Catalytic transformations involving small organic molecules, known as 'organocatalysis', have attracted much interest in recent years.[1] These catalysts are environmentally more benign, as they do not involve metals. The heterogenization of organocatalysts provides additional advantages, such as the ready separation of products and the reusability of catalysts, which are very important in large scale production. Strategies involving the functionalization of both inorganic and polymer supports with organic catalysts have been reported recently.[2] The synthesis of these supports involve either high temperature calcinations of metal-oxo/hydroxo derivatives or polymerization of petrochemical feed stocks.

In recent years, the emphasis of science and technology has shifted more towards environmentally friendly and sustainable resources and processes; in this regard, direct utilization of natural materials for catalytic applications is a very attractive strategy. In particular, biopolymers are important candidates to explore for catalysis.

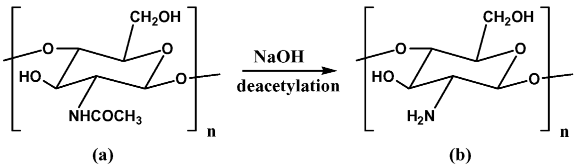
Biopolymers are a diverse and versatile class of materials that are cheap and widely abundant in nature.[3] These renewable, biodegradable and biocompatible materials have potential applications as adhesives, absorbents, lubricants and soil conditioners, and in cosmetics, drug delivery, textiles and high strength structural materials.[4] In recent years, these materials have attracted great interest as supports for catalytic reactions. Among biopolymers, chitosan is the most widely used support for catalytic applications.[5] Chitosan is produced by alkaline deacetylation of chitin (Scheme 1), the most abundant biopolymer in nature after cellulose. The presence of both hydroxyl and amino groups make it useful as a chelating agent. Therefore, most studies have focused on exploiting the complexation properties of chitosan with metal ions in heterogeneous molecular catalysis.[6] Although chitosan can be considered as a natural polyamine, the direct use of this polymer in base catalysis is not well explored. Recently, Quignard and coworkers showed that chitosan microspheres, obtained under supercritical CO_2 conditions, could be used as a catalyst for the synthesis of monoglyceride by fatty acid addition to glycidol.[7]

As a part of our ongoing efforts to develop biopolymers for catalytic applications, we have recently reported cellulose-supported Cu and Pd catalysts for C–N and C–C coupling reactions.[8] In this communication, we wish to report the use of chitosan hydrogel as an efficient base catalyst for aldol and Knoevenagel reactions (Scheme 2).

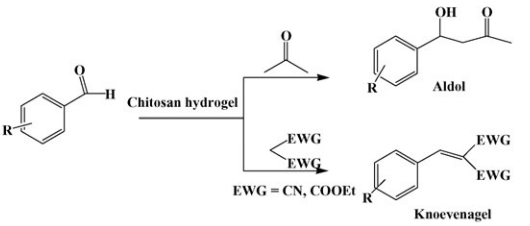
The preparation of chitosan hydrogel beads is rather simple, and accomplished by adapting a reported procedure.[9] The as-prepared beads could be directly used in the catalytic experiments.

The initial aldol reaction was performed by combining *para*-nitrobenzaldehyde (1 mmol), acetone (1 mL) and chitosan gel beads (20 units) in DMSO (4 mL) at room temperature (Scheme 2).[10] Stirring the reaction mixture for 18 h provided a quantitative conversion of the aldehyde, with a selectivity of 90 : 10 for aldol *vs.* dehydration products (Fig. 1A). No product formation was observed when the reaction was conducted under similar conditions with dried gel beads or commercial chitosan (Fig. 1B and 1C). It was observed that the solvent plays a major role in the selectivity of the aldol product. For example, the selectivity between aldol *vs.* dehydration products dropped from 90 : 10 in DMSO to 67 : 33 and 59 : 41 in MeOH and H_2O, respectively (Fig. 1D and 1E).

Next, different substrates were examined, and the results are summarized in Table 1. The aromatic aldehydes, having an electron-withdrawing substituent, gave the corresponding aldol products in high yields with good selectivities (Table 1,



Scheme 1 The chemical structures of (a) chitin and (b) chitosan.



Scheme 2 Chitosan hydrogel-catalyzed aldol and Knoevenagel reactions.

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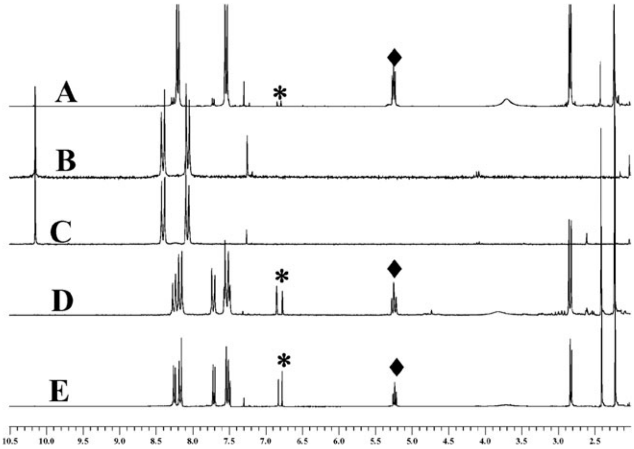
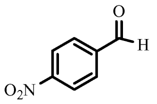
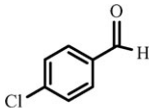
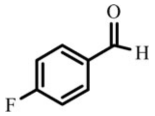
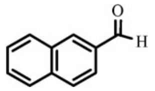
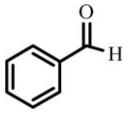
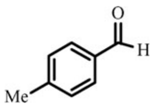
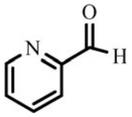
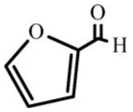


Fig. 1 ^{1}H NMR spectra of reaction mixtures of *para*-nitrobenzaldehyde and acetone catalyzed by (A) chitosan hydrogel in DMSO, (B) dried chitosan hydrogel, (C) commercial chitosan, (D) chitosan hydrogel in MeOH and (E) chitosan hydrogel in H_2O (◆ corresponds to the aldol product; * corresponds to the dehydration product).

Table 1 Chitosan hydrogel-catalyzed aldol reactions between acetone and aromatic aldehydes in DMSO[a]

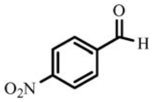
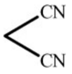
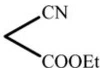
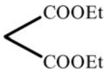
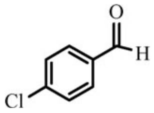
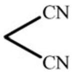
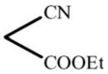
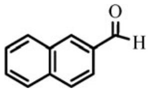
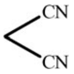
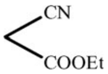
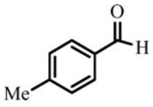
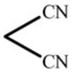
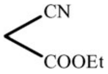
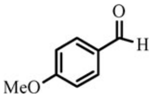
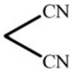
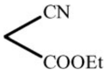
Entry	Aldehyde	Conversion (%)[b]	Selectivity[c] aldol/dehydration
1		100	90/10
2		86	96/4
3		82	94/6
4		95	94/6
5		23	100/0
6		—	—
7		100	21/79
8		100	8/92

[a] Reaction conditions: Aldehyde (1 mmol), acetone (1 mL), DMSO (4 mL), chitosan gel beads (20 units), rt, 18 h. [b] NMR yield based on aromatic aldehyde. [c] Based on NMR.

entries 1–3). 2-Napthaldehyde also provided higher conversion (Table 1, entry 4), whereas benzaldehyde gave a lower conversion (Table 1, entry 5). No product formation was observed with *para*-tolualdehyde, which has an electron-donating methyl group (Table 1, entry 6). In contrast, the reaction of acetone with heteroaromatic aldehydes provided higher dehydration products (Table 1, entries 7 and 8). Reactions of *n*-butyraldehyde (enolizable), trimethylacetaldehyde (non-enolizable) and *trans*-cinnamaldehyde with acetone were unsuccessful under similar reaction conditions. Furthermore, hydroxyacetone and cyclohexanone were tested as donors in place of acetone. No reaction was observed with hydroxyacetone, whereas cyclohexanone provided 77% aldol product exclusively upon reaction with *para*-nitrobenzaldehyde, showing a 2 : 1 *syn vs. anti* diastereoselectivity. Optical rotations were checked for the products of Table 1, entries 1 and 4. Unfortunately, we could not obtain any induction of stereoselectivity because of the backbone chirality of the chitosan polymer. The present chitosan hydrogels behave more like a supported base. Higher accessibility of the amine functional groups in the hydrogel, which has a porous network, unlike to the commercial material and dried chitosan beads, may be responsible for the higher activity observed. Accessible free amines were determined by reacting chitosan with salicylaldehyde to form a Schiff base complex, and analysing the remaining unreacted salicylaldehyde by GC, using nitrobenzene as an internal standard.[11] Accessible free amines in chitosan hydrogel beads, commercial chitosan and dried chitosan beads were 55–65, 2.5 and 1.65%, respectively, based on an average of 80% deacetylated units in commercial chitosan.

This natural polymer base was further tested for Knoevenagel condensations at room temperature involving various aromatic carbonyl compounds, with malononitrile, ethylcyanoacetate and diethylmalonate as the active methylene compounds (Table 2). The aromatic aldehydes readily condensed with malononitrile and ethyl cyanoacetate, whereas the reaction with diethylmalonate yielded only the aldol addition product. This may be attributed to the lower acidity associated with diethylmalonate compared to malononitrile and ethylcyanoacetate. All the reactions proceeded selectively to the dehydrated products without any side reactions in DMSO, as can be seen in Table 2. No self-condensation or Cannizaro products were obtained. It was observed that aromatic aldehydes having either electron withdrawing or electron donating

Table 2 Chitosan hydrogel-catalyzed Knoevenagel reactions between aromatic aldehydes and different donors in DMSO[a]

Entry	Aldehyde	Donor	Time/min	Conversion (%)[b]	Selectivity (%)[c]
1			3	100	100
2	〃		5	100 (40)	100
3	〃		18[d]	83	100[d]
4			3	100	100
5	〃		5	100	100
6			3	100	100
7	〃		5	100	100
8			5	100	100
9	〃		10	100	100
10			5	100	100
11	〃		10	72 (0)	100

[a] Reaction conditions: Aldehyde (1 mmol), donor (1.1 mmol), DMSO (3 mL), chitosan gel beads (20 units), rt. [b] NMR yield based on aromatic aldehyde; values in parentheses correspond to blank reactions. [c] Based on NMR. [d] Aldol product after 18 h.

groups provided Knoevenagel products in high yields, exclusively.

We further tested the efficacy of the present catalyst in terms of its reusability in aldol and Knoevenagel reactions. After completion of the reactions, the chitosan gel beads were filtered and washed with DMSO, and used directly for further recycling experiments. Three consecutive recycling experiments between *para*-nitrobenzaldehyde and acetone provided 87.2, 86.3 and 86.0% isolated yields of the aldol products. Similarly, the reaction between *para*-nitrobenzaldehyde and malononitrile provided quantitative conversion of the Knoevenagel products in three cycles, as observed by ^{1}H NMR spectroscopy.

In conclusion, we have successfully utilized chitosan hydrogels as a heterogeneous base organocatalyst for aldol and Knoevenagel reactions, providing the products in high yields and with high chemoselectivity. The catalyst was recovered by simple filtration and reused several times without a significant loss in activity. The application of the present catalyst to other base-catalyzed C–C coupling reactions is currently under investigation, and results will be published in due course.

Experimental

Low molecular weight chitosan [75–85% deacetylated, viscosity 20–200 cP (1% solution in 1% acetic acid, Brookfield)], hydroxyacetone and the aromatic aldehydes were purchased from Aldrich. Malononitrile, ethylcyanoacetate, diethylmalonate, cyclohexanone and acetone were purchased from S. D. Fine-Chem, India. ^{1}H NMR spectra were determined on a Bruker spectrometer (300 MHz) with TMS as the internal standard.

Syntheses

General procedure for the preparation of chitosan hydrogel beads. The chitosan hydrogel beads were prepared by adapting the copper-chitosan procedure reported in the literature.[9] 0.32 g of low molecular weight chitosan was dissolved in 0.1 M HCl (20 mL) at room temperature and stirred until the formation of a clear solution. The chitosan solution was poured dropwise into 0.1 M NaOH solution (300 mL), resulting in the immediate coagulation of the droplets into uniform beads. The beads were matured for 1 h without stirring, collected in a Buchner funnel and washed with excess distilled water until the filtrate was neutral to phenolphthalein indicator. These hydrogel beads were directly used in the catalytic experiments.

Quantitative GC analysis of free amines in chitosan beads. In a typical experiment, 20 units of chitosan hydrogel beads were taken into 2.5 mL of a solution of salicylaldehyde (0.16 mol L^{-1}) in ethanol to form a Schiff base complex. Accessible free amines were determined by analysing the remaining unreacted salicylaldehyde by GC, using nitrobenzene as the internal standard.[11] Accessible free amines in chitosan hydrogel beads, commercial chitosan and dried chitosan beads were 55–65, 2.5 and 1.65%, respectively, based on an average of 80% deacetylated units in commercial chitosan.

Catalytic studies

Typical procedure for an aldol reaction catalysed by chitosan hydrogel beads. Chitosan hydrogel beads (20 units), *para*-nitrobenzaldehyde (1 mmol), acetone (1 mL) and DMSO (4 mL) were placed in a round-bottomed flask and stirred at room temperature for 18 h. The resulting reaction mixture was filtered to remove the catalyst, and the filtrate was extracted with ethyl acetate and washed with water. The organic portion was separated and evaporated under vacuum to obtain the crude products.

Typical procedure for a Knoevenagel reaction catalysed by chitosan hydrogel beads. A similar procedure to that described above for aldol reactions was employed, except that in place of acetone, an active methylene compound (malononitrile, 1.1 mmol) was added and stirred until the completion of the reaction, as monitored by thin layer chromatography (TLC).

The filtered catalysts were used directly for further recycling experiments.

Table 1, entry 1: Isolated yield: 87.2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.5 Hz, 1 H), 7.55 (d, J = 8.5 Hz, 1 H), 5.25 (m, 1 H), 3.56 (br, 1 H), 2.85 (m, 2 H) and 2.25 (s, 3 H).

Table 2, entry 1: Isolated yield = 96.4%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 8.7 Hz, 2 H, Ar), 8.09 (d, J = 8.7 Hz, 2 H, Ar) and 7.88 (s, 1 H).

Acknowledgements

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References

1 (*a*) A. Berkessel, in *Asymmetric Organocatalysis*, ed. H. Groger, Wiley-VCH, Weinheim, 2005, pp. 203; (*b*) B. List, *Tetrahedron*, 2002, **58**, 5573; (*c*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138.

2 (*a*) M. Benaglia, A. Puglisi and F. Cozzi, *Chem. Rev.*, 2003, **103**, 3401; (*b*) Y. Wang, H. Jiang, H. Liua and P. Liu, *Tetrahedron Lett.*, 2005, **46**, 3935; (*c*) C. Ogawa, M. Sugiura and S. Kobayashi, *Chem. Commun.*, 2003, 192; (*d*) H. Hagiwara, J. Hamaya, T. Hoshi and C. Yokoyama, *Tetrahedron Lett.*, 2005, **46**, 393; (*e*) H. S. Kim, Y. M. Song, J. S. Choi, J. W. Yang and H. Han, *Tetrahedron*, 2004, **60**, 2051.

3 D. L. Kaplan, *Biopolymers from Renewable Resources*, Springer-Verlag, Berlin, 1998.

4 (*a*) H. Sashiwa and S. Aiba, *Prog. Polym. Sci.*, 2004, **29**, 887; (*b*) M. N. V. Ravi Kumar, *React. Funct. Polym.*, 2000, **46**, 1.

5 (*a*) E. Guibal, *Prog. Polym. Sci.*, 2005, **30**, 71; (*b*) D. J. Macquarrie and J. J. E. Hardy, *Ind. Eng. Chem. Res.*, 2005, **44**, 8499.

6 (*a*) L. F. Xiao, F. W. Li and C. G. Xia, *Appl. Catal., A*, 2005, **279**, 125; (*b*) G. Huai-min and C. Xian-su, *Polym. Adv. Technol.*, 2004, **15**, 89; (*c*) F. Quignard, A. Choplin and A. Domard, *Langmuir*, 2000, **16**, 9106; (*d*) J. J. E. Hardy, S. Hubert, D. J. Macquarrie and A. J. Wilson, *Green Chem.*, 2004, **6**, 53.

7 R. Valentin, K. Molvinger, F. Quignard and D. Brunel, *New J. Chem.*, 2003, **27**, 1690.

8 (*a*) K. R. Reddy, N. S. Kumar, P. S. Reddy, B. Sreedhar and M. Lakshmi Kantam, *J. Mol. Catal. A: Chem.*, 2006, **252**, 12; (*b*) K. R. Reddy, N. S. Kumar, B. Sreedhar and M. Lakshmi Kantam, *J. Mol. Catal. A: Chem.*, 2006, **252**, 136.

9 A. V. Kucherov, N. V. Kramareva, E. D. Finashina, A. E. Koklin and L. M. Kustov, *J. Mol. Catal. A: Chem.*, 2003, **198**, 333.

10 The average dried weight of 20 units of the chitosan hydrogel beads is 33 mg, which corresponds to 0.2 mmol of the catalyst. However, based on the active accessible free amine groups, as reported in the experimental section (55–65%), the active catalyst for 20 units will be in the range 11–13 mol% with respect to the aldehyde.

11 T. G. Waddell, D. E. Leyden and M. T. Debello, *J. Am. Chem. Soc.*, 1981, **103**, 5303.