Study of the Michael addition of β-cyclodextrin–thiol complexes to conjugated alkenes in water†

N. Srilakshmi Krishnaveni, K. Surendra and K. Rama Rao*

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An environmentally benign and highly efficient supramolecular Michael addition of thiols from the secondary side of β-cyclodextrin to α,β-unsaturated compounds at the primary side in water is described in quantitative yields; products of undesirable side reactions resulting from polymerization are not observed; the use of cyclodextrin precludes the use of either acid or base and the catalyst can be recovered and reused.

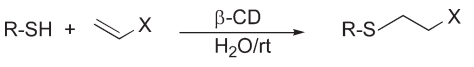
The Michael reaction since its discovery in 1889 is one of the most important reactions in organic chemistry.[1] The conjugate addition of thiols to electron deficient olefins to form a carbon–sulfur bond constitutes a key reaction in biosynthesis as well as in organic synthesis.[2] The organosulfur compounds are also useful in the synthesis of biologically active compounds such as the calcium antagonist diltiazem.[3] Consequently, a large number of reagents have been reported in the literature for the addition of mercaptans to conjugated alkenes.[4] However, to avoid side reactions, several inorganic salts have been introduced in the presence of strong acid or base.[5] A number of procedures either based on activation of thiol by a base or activation of the acceptor olefins with Lewis acids are used.[6] More recently tetrabutylammonium halides have been used as phase transfer catalysts.[7] The use of strong acids (polymerization of vinyl ketones) and bases in the medium, toxic catalysts, harsh conditions, far from satisfactory yields and selectivities due to the occurrence of side reactions make these methods lack any practical application in industry. Recently, there is also a report of carrying out these reactions in ionic liquids[8] and a mixture of ionic liquids and water (2:1).[9] These ionic liquids have been shown to have serious drawbacks, especially imidazolium ones with PF_6 and BF_4 anions, as they are as toxic as benzene in certain aquatic ecosystems and also liberate hazardous HF during recycling.[10] Apart from this, the high cost[11] and disposability of these solvents also limit their utility. Moreover, these reactions were unsuccessful in water alone.

With green chemistry becoming a central issue in both academic and industrial research in the 21st century,[12] the development of environmentally benign and clean synthetic procedures has become the goal of present day organic synthesis. Thus, there is need for developing Michael addition in water with a recyclable catalyst and without the use of any harmful organic solvents since water is a safe, economical and environmentally benign solvent.[13] To achieve these ideal conditions, the best choice appeared to be through supramolecular catalysis involving cyclodextrins using water as solvent.

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes by non-covalent bonding as seen in enzymes.[14] Complexation depends on the size, shape and hydrophobicity of the guest molecule. Thus mimicking of biochemical selectivity, which is due to orientation of the substrate by complex formation positioning only a certain region for favorable attack, will be superior to chemical selectivity, which involves random attack due to intrinsic reactivity of the substrate at different regions. Our earlier expertise in the field of biomimetic modelling of organic chemical reactions involving cyclodextrins[15] prompted us to attempt the Michael addition of various thiols to conjugated alkenes under biomimetic conditions using cyclodextrins with water as a solvent at room temperature (Scheme 1). Such reactions also do not generate any toxic waste products.

The reaction was carried out as follows: β-CD (1 mmol) was dissolved in water (15 ml) by warming to 60 °C until a clear solution was formed, then thiophenol (1 mmol) dissolved in acetone (1 ml) was added dropwise and allowed to cool to room temperature. The alkene (1.1 mmol) was then added and stirred at room temperature until the reaction was complete (Table 1). The organic material was extracted with ethyl acetate, dried and concentrated under reduced pressure and the resulting product though seen as a single compound by TLC, was further purified by passing over a column of silica gel. CD was recovered by filtration and reused. The yields were almost quantitative.

This is the first practically feasible Michael addition reaction of thiols with a variety of conjugated alkenes in water. The reaction proceeds efficiently at room temperature without the need of any acid or base catalyst. The reaction goes to completion in a short time (5–45 min). This methodology is compatible with various α,β-unsaturated ketones, aldehydes, esters, nitriles and amides and different substituted aromatic thiols and cyclohexanethiol under mild reaction conditions. No byproduct formation was observed. Moreover, these reactions are clean with nearly quantitative yields compared to conventional methods, shorter reaction times, higher selectivities and recyclable catalyst. While these reactions do take place with α-CD, β-CD was chosen as the catalyst since it is

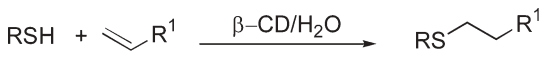


R=aryl, cyclohexyl
X=CHO,COMe,CN,CO_2Me,$CONH_2$

Scheme 1

† IICT communication no. 040936.
*drkrrao@yahoo.com

Table 1 Michael addition of thiols to conjugated alkenes using β-CD in water



Entry	R	R^1	Time/min	Yield[a,b] (%)
1	Ph	CHO	5	95
2	Ph	COMe	5	98
3	Ph	COMe	5	98[c]
4	Ph	CN	10	97
5	Ph	CO_2Me	10	96
6	Ph	$CONH_2$	15	96
7	*p*-ClC_6H_4	CHO	5	95
8	*p*-ClC_6H_4	COMe	5	98
9	*p*-ClC_6H_4	CN	10	96
10	*p*-ClC_6H_4	CO_2Me	10	95
11	*p*-ClC_6H_4	$CONH_2$	15	94
12	*o*-MeC_6H_4	CHO	5	92
13	*o*-MeC_6H_4	COMe	5	97
14	*o*-MeC_6H_4	CN	10	95
15	*o*-MeC_6H_4	CO_2Me	10	94
16	*o*-MeC_6H_4	$CONH_2$	15	92
17	*p*-$MeOC_6H_4$	CHO	5	90
18	*p*-$MeOC_6H_4$	COMe	5	96
19	*p*-$MeOC_6H_4$	CN	10	95
20	*p*-$MeOC_6H_4$	CO_2Me	10	94
21	*p*-$MeOC_6H_4$	$CONH_2$	15	92
22	C_6H_{12}	COMe	25	95
23	C_6H_{12}	CN	30	92
24	C_6H_{12}	$CONH_2$	45	90

[a] All the products were characterized by mass, ^{1}H NMR, IR spectroscopy and compared with known compounds.[8] [b] Isolated yields. [c] Catalyst was recovered and reused for three consecutive runs in this reaction without change in the yield and purity.

inexpensive and easily accessible. In an earlier report by Sakuraba *et al*, Michael addition of thiols to 2-cyclohexenone and maleic acid esters in the presence of cyclodextrin had been shown to take unusually long reaction times of over seven days.[16]

The catalytic activity of cyclodextrins for these Michael additions is established by the fact that no reaction was observed in the absence of cyclodextrin. The mechanism of addition of thiols as β-cyclodextrin complexes to conjugated alkenes was postulated *via* convincing evidence from ^{1}H NMR spectroscopy. The hydrogen bonding of thiols with the CD hydroxyl makes the S–H bond weaker enhancing the nucleophilicity of sulfur and making it a better nucleophile towards addition to electron deficient alkenes. Using thiophenol and methyl vinyl ketone (MVK) as a representative example, a comparison of the ^{1}H NMR spectra (D_2O) of β-CD, β-CD–thiophenol complex and a freeze-dried reaction mixture of the thiophenol–CD complex with MVK at 3 min were studied. It could be observed from Fig. 1 that there is an upfield shift of H_3 (0.018 ppm) and H_5 (0.015 ppm) protons of cyclodextrin in the β-CD–thiophenol complex as compared to β-CD, indicating the formation of an inclusion complex of thiophenol with β-CD.[17] It is further observed from the spectra of the reaction mixture of β-CD–thiophenol complex and MVK at 3 min that there is also an upfield shift of the H_6 proton by 0.028 ppm. This indicates the complexation of MVK from the primary side of the cyclodextrin. Thus, it is deduced from these ^{1}H NMR studies that while the thiophenol is still being retained in the hydrophobic cavity of β-CD, MVK complexes from the primary side of β-cyclodextrin for the reaction to proceed (Fig. 2).

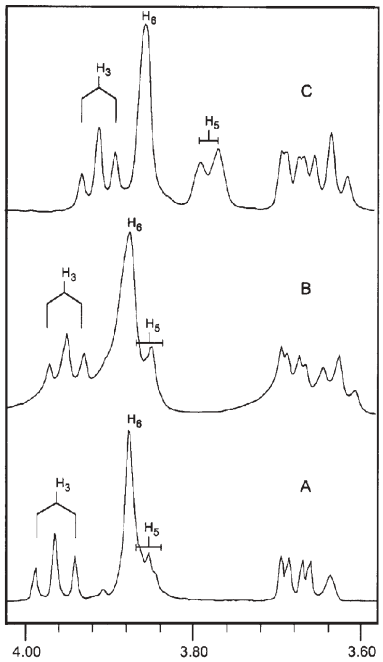


Fig. 1 ^{1}H NMR spectra (D_2O) of (A) β-CD, (B) β-CD–thiophenol complex (C) and a freeze-dried reaction mixture of the thiophenol–CD complex with MVK at 3 min (D).

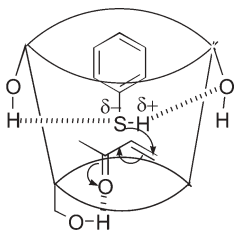


Fig. 2

This shows in a very elegant way how the olefin is set for the addition reaction with the thiol nucleophile in the hydrophobic cavity of β-cyclodextrin.

These CD mediated water solvent reactions are very useful both from economical and environmental points of view. β-Cyclodextrin, apart from being non-toxic is also considered as metabolically safe.[18] In contrast with the existing methods using many acidic catalysts, this method is very simple, high yielding and environfriendly. Significant improvements offered by this procedure are: (i) fast reaction (time), (ii) simple operational and mild conditions (room temperature), (iii) excellent yields, (iv) cost efficiency providing recyclability of the catalyst and (v) green aspect avoiding hazardous organic solvents, toxic and expensive reagents. Further potential applications of this reaction are under study.

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N. Srilakshmi Krishnaveni, K. Surendra and K. Rama Rao*
Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India. E-mail: drkrrao@yahoo.com

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