β-Cyclodextrin-Promoted Addition of Benzeneselenol to Conjugated Alkenes in Water

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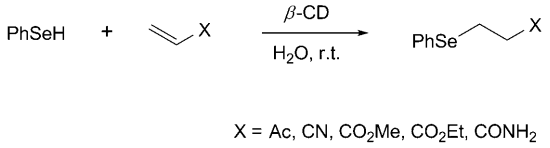
For the first time, a mild and efficient procedure was developed for the conjugate addition of α,β-unsaturated compounds to benzeneselenol providing β-(phenylseleno)-substituted compounds (*Scheme*). The reaction was promoted by β-cyclodextrin, proceeded in H_2O at room temperature, and gave impressive yields (*Table*). The mechanism of the addition reaction, taking place within the cyclodextrin cavity, was supported by the analysis of the guests and host signals in the ^{1}H-NMR spectra (*Fig. 1*).

Introduction. – C–Se Bond containing compounds are of great importance in organic synthesis as key intermediates in various reactions [1]. In particular, β-(phenylseleno)-substituted carbonyl compounds are well established as potential enone β-anion equivalents [2]; however, the reported methodologies for the synthesis of these compounds are very limited [3]. In general, β-(phenylseleno)-substituted carbonyl compounds are synthesized by the conjugate addition of benzeneselenol generated *in situ* from diphenyl diselenide to olefins [4]. Even in these reactions, the yields are not satisfactory, being low to moderate in most of the cases, and anhydrous solvents and toxic reagents are involved. These conjugate additions also proceed by the *in situ* formation of benzeneselenol from diphenyl diselenide in the presence of catalysts such as La/I_2 [5a], Na/Me_3SiCl [5b], In/Me_3SiCl [5c], *etc.* Apart from this, benzeneselenol itself is sensitive to air [5d]. Thus, in view of these shortcomings, there is a need to develop a mild and environmentally friendly synthetic procedure for these high-value compounds, starting directly from benzeneselenol, if possible, and replacing organic solvents, most of which are flammable, toxic, or carcinogenic, by H_2O in the presence of a recyclable activator as part of a green-chemical approach [6]. To achieve these ideal conditions, the best choice appeared to be a supramolecular catalysis involving cyclodextrins wherein benzeneselenol can be encapsulated in the hydrophobic cavity thus allowing to carry out the reaction in H_2O.

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 noncovalent bonding as seen in enzymes. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus, mimicking biochemical selectivity, which is due to the orientation of the substrate by complex formation thus making available only certain regions of the guest to a favorable attack,

will be superior to chemical selectivity which involves random attack. Our earlier expertise in the field of biomimetic modeling of organic chemical reactions involving cyclodextrins [7] prompted us to attempt the conjugate addition of olefins to benzeneselenol under biomimetic conditions in the presence of cyclodextrins and in the solvent H_2O at room temperature (*Scheme*).

Scheme. *Addition of Benzeneselenol to Conjugated Alkenes*

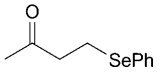
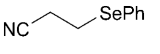
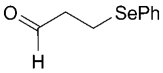
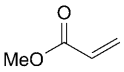
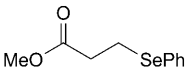
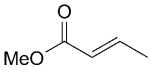
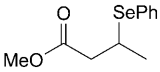
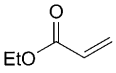
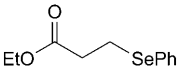
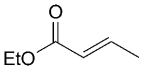
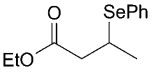
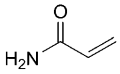
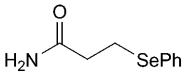
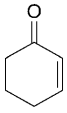
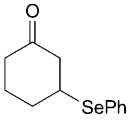
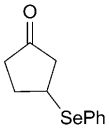


Results and Discussions. – In general, the conjugate addition reaction was carried out by dissolving β-cyclodextrin (β-CD) in H_2O and then adding successively the benzeneselenol and the olefin while stirring at room temperature to give the corresponding *Michael* adduct in impressive yields (*Table*). The reaction went on smoothly at room temperature. The catalyst β-CD was easily recovered and could be reused. Though a β-CD complex with benzeneselenol was formed *in situ*, it was prepared separately, and the ratio β-CD/benzeneselenol was found to be 1:1 from the amount of benzeneselenol extracted from the known amount of the complex. These addition reactions did not proceed in the absence of β-CD. The products were characterized by their ^{1}H-NMR, MS, and IR data and compared with the known compounds [4] (see the *Table*).

This is the first practically feasible conjugate addition of benzeneselenol with a variety of conjugated alkenes in H_2O, proceeding efficiently at room temperature without the need of any acid or base catalyst. The methodology can be applied to various α,β-unsaturated ketones, esters, and nitriles under mild reaction conditions. Moreover, these conjugate additions are clean with impressive yields compared to conventional methods, have shorter reaction times and higher selectivities, and involve a recyclable catalyst [7].

In this new biomimetic methodology, the catalyst β-CD plays a decisive role not only by activating the benzeneselenol but also by promoting its conjugate addition due to the formation of an inclusion complex. The mode of addition of benzeneselenol to α,β-unsaturated alkenes *via* the β-CD complex was deduced from a ^{1}H-NMR analysis, one of the most important techniques used for the characterization of inclusion complexes, by revealing chemical-shift changes in the resonances of the host (β-CD) and the guest protons [7][8]. Thus, a comparison of the ^{1}H-NMR spectra (D_2O; *Fig. 1*) of β-CD and of the β-CD/benzeneselenol complex showed an upfield shift of H–C(3) ($\Delta\delta$ 0.02) and H–C(5) ($\Delta\delta$ 0.018) of β-CD in the β-CD/benzeneselenol complex as compared to β-CD, indicating the formation of an inclusion complex of benzeneselenol from the secondary (more open) side of β-CD. An upfield shift of CH_2(6) of β-CD ($\Delta\delta$ 0.034) was further observed in the spectra of the freeze-dried reaction mixture of the β-CD/benzeneselenol complex with methyl vinyl ketone (MVK) after 15 min, indicating that the complexation of MVK takes place from the primary (more closed) side of β-

Table. *Addition of Benzeneselenol to Conjugated Olefines in H_2O in the Presence of β-CD*

Entry	Olefine	Product	Time [min]	Yield [%]	Ref.
1			20	88	[4g]
2			25	86	[4a]
3			20	85	[4a]
4			25	86	[4a]
5			45	82	[4a]
6			25	86	[4a]
7			45	80	[4a]
8			30	80	–
9			45	82	[4g]
10			45	80	[4g]

CD. These ^{1}H-NMR data clearly demonstrate that the MVK is elegantly set for the addition reaction with the benzeneselenol in the hydrophobic microenvironment of the β-CD cavity (*Fig. 2*).

Conclusions. – The β-CD mediated addition reactions of benzeneselenol to conjugated alkenes in H_2O are very useful both from an economical and an environmental point of view. β-CD, apart from being nontoxic, is also considered as metabolically safe [9]. In contrast to the existing addition reactions with diselenides, which are activated by metal catalysts, our addition reaction is a straightforward transformation starting directly from benzeneselenol and the alkene in the solvent H_2O and in the presence of β-CD as the reusable catalyst.

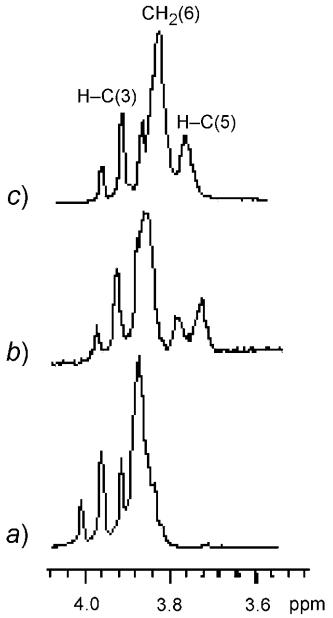


Fig. 1. *^{1}H-NMR Spectra* (D_2O, 25°) *of* a) *β-CD,* b) *the β-CD/benzeneselenol complex, and* c) *the reaction mixture of the β-CD/benzeneselenol complex and methyl vinyl ketone after 15 min*

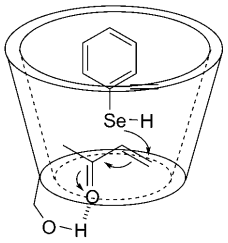


Fig. 2. *Supramolecular addition of benzeneselenol to conjugated alkenes within β-CD*

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Experimental Part

General. All reactions were carried out in an atmosphere of air without any special precautions. Chemicals were purchased from *Aldrich* and *S. D. Fine Chemicals* and used as received. ^{1}H-NMR Spectra: *Varian 200* or *Brucker 300* spectrometer; δ in ppm rel. to Me_4Si as internal standard, J in Hz. IR Spectra: *Nicolet* FT-IR spectrometer; in cm^{-1}. MS: *V.G.-Auto* spectrometer; in m/z (rel. %).

General Procedure. Procedure exemplified by 3-(phenylseleno)propanamide (*Table, Entry 8*): To a soln. of β-CD (113.4 mg, 0.1 mmol) in H_2O (15 ml), benzeneselenol (106 µl, 1 mmol) in acetone (1 ml) was added dropwise at r.t. Prop-2-enamide (71 mg, 1 mmol) was then added and stirred until the reaction was complete (*Table*). The org. material was extracted with AcOEt, the extract dried and concentrated, and the resulting crude product further purified by recrystallization from AcOEt: 182 mg (80%) of pure 3-(phenylseleno)propanamide. White solid. HPLC (C_{18} column, H_2O/MeCN 7:3 with 0.1% H_3PO_4, flow

rate 0.7 ml/min, det. at 220 nm): purity >98%. M.p. 103–105°. IR: 3375, 3182, 2929, 1652. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.60 (*t*, *J* = 7.5, 15.1, 2 H); 3.14 (*t*, *J* = 7.6, 14.3, 2 H); 5.58 (br., NH_2); 7.22–7.33 (*m*, 3 H); 7.45–7.57 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23; 36; 127; 128; 129; 133; 174. MS: 229 ([*M* + H]$^+$). Anal. calc. for $C_9H_{11}NOSe$ (228.15): C 47.38, H 4.86; found: C 47.35, H 4.95.

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