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Catalytic Synthesis of 1-Arylethylphosphonates by the Hydrogenation of Unsaturated Precursors in the Presence of Chitosan-Based Palladium Catalysts

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Abstract—Three-component silica-supported palladium-containing systems based on chitosan were synthesized and studied by scanning electron microscopy. These systems showed catalytic activity in the hydrogenation (including chemoselective hydrogenation) of α,β-unsaturated phosphonic acids and their esters. Modification of chitosan on the silica surface with glutaraldehyde considerably enhances the stability and activity of the catalyst.

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Up-to-date requirements imposed on selective catalytic hydrogenation processes imply not only high performance and selectivity but primarily their compliance with ecologically clean technology standards (such as recycling of the catalyst, wastelessness, and use of ecologically safe solvents). A possible way of solving this problem consists of development of new catalytic systems on the basis of transition metal complexes immobilized on various polymeric supports, including organic ones. In the recent years, biopolymers (specifically polysaccharides such as cellulose, chitin, and chitosan) have received wide application for heterogenization of homogeneous catalysts.

Chitosan is a linear polysaccharide whose polymeric chain consists of β-1,4-connected glucosamine residues. The source of chitosan is chitin; the latter in turn is isolated from shells of shrimps, crabs, and other *Arthropoda* species, the overall number of which is tremendous. Among all kinds of amended organic resources, stocks of chitin are comparable only with those of cellulose. Taking into account unique properties of chitosan, the following its potential advantages as support for metal complexes should be noted [1–3]: (1) complete absence of toxicity, the ability to undergo biodegradation, and compatibility with cells of any plant or animal; (2) the ability to ensure high metal dispersity over the support surface, for chelated metal ion appears to be isolated from the neighboring metal ions; (3) the presence of various functional groups, which makes it possible to use chitosan without preliminary modification (in contrast, cellulose cannot be used as support unless preliminarily phosphorylated); (4) easy regeneration from waste catalyst of high-cost components by burning the organic support and subsequent extraction; (5) the presence of chiral carbon atoms in a monomer unit of chitosan.

Chitosan is widely used in various fields of chemistry [4], including catalysis [5]. Some examples of application of chitosan complexes with platinum metals as catalysts for selective liquid-phase hydrogenation of polyunsaturated and polyfunctional compounds have been reported [5–8].

The goal of the present study was to search for new effective heterogeneous (recyclable) chitosan-based catalytic systems for selective hydrogenation of α,β-unsaturated 1-arylethenylphosphonic acids and their esters. The latter were selected as model substrates, taking into account the known biological activity of the corresponding reduction products, 1-arylethylphosphonates, which are phosphorus-containing analogs of 2-arylpropionic acids constituting a class of nonsteroid antiphlogistic and analgetic drugs, such as Naproxen and Ibuprofen. There are published data according to which 1-arylethylphosphones exhibit negative inotrop-

ic [9], Ca^{2+}-antagonistic [9, 10], neuroprotective [10], and psychotropic activity [10], inhibit cyclooxygenase [11], and act as reactive immunization haptenes [12, 13]. Oxovanadium 1-arylethylphosphonates were shown to have a layered structure which makes these compounds promising for design of functional materials [14]. Finally, 1-arylethylphosphonates are widely used in synthetic practice, in particular as reagents in the Horner reactions.

We previously proposed a convenient general procedure for the synthesis of 1-arylethylphosphonic acids and their esters via catalytic reduction of accessible α,β-unsaturated precursors with ammonium formate in the presence of Pd/C [15]. The reduction of 1-arylethenylphosphonates with molecular hydrogen was performed for the first time using [Pd(*t*-Bu_2PO_2)-(*t*-Bu_2PO)(*t*-Bu_2POH)] as homogeneous palladium catalyst and diethyl and diphenyl 1-phenylethenylphosphonates as examples [16]. Stereoselective homogeneous hydrogenation of a series of 1-arylethenylphosphonic acids and their esters over chiral ruthenium [15, 17] and iridium complexes [18] was also reported.

Aldea and Alper [19] made an attempt to use heterogeneous catalysts in the reduction of α,β-unsaturated phosphonates; the authors showed that the hydrogenation of diethyl ethenylphosphonate smoothly occurs in the presence of a ruthenium complex immobilized on the surface of modified montmorillonite [19]. An undoubted advantage of this procedure is that no removal of the ruthenium complex from the support was observed during the catalytic process; therefore, the catalyst can be reused. However, the authors did not succeed in extending the developed hydrogenation procedure to other unsaturated phosphonates, for introduction of substituents to the double-bonded carbon atoms inhibited the reduction process. For example, 1-phenylethenylphosphonate and prop-1-enylphosphonate turned out to be completely inactive under the above conditions.

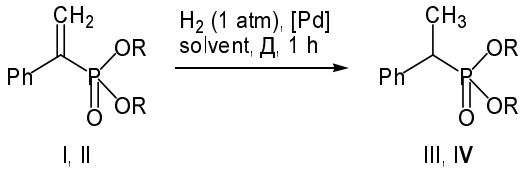
In the present work we used as model substrates 1-phenylethenylphosphonic acid (**I**) and its diethyl ester **II** to estimate the efficiency of palladium-containing systems on the basis of chitosan in the catalytic hydrogenation of 1-arylethenylphosphonates. The reactions were carried out in a boiling solvent (water, methanol, or ethanol) at a hydrogen pressure equal to atmospheric (1 atm). The progress of reactions was monitored by ^{31}P NMR spectroscopy, following disappearance of the signals belonging to initial compounds **I** (δ_P 15.9 ppm, CD_3OD) and **II** (δ_P 17.1 ppm, CD_3OD) and accumulation of signals from the target products, 1-phenylethylphosphonic acid **III** (δ_P 29.9 ppm, CD_3OD) and its diethyl ester **IV** (δ_P 30.2 ppm, CD_3OD). The results are collected in table (Scheme 1).

Hydrogenation of 1-phenylethenylphosphonic acid (**I**) and diethyl 1-phenylethenylphosphonate (**II**) in the presence of palladium catalysts based on chitosan and its derivatives

Run no.	Substrate	Catalyst	Pd, mol %	Solvent	Yield, %
1	**I**	**A1**	0.9	H_2O	100
2	**I**	**A2**	0.9	H_2O	77 (100[a])
3	**I**	**A1**	0.9	MeOH	94 (30[b])
4	**I**	**A2**	0.9	EtOH	8
5	**II**	**A2**	1.1	MeOH	0
6	**II**	**A2**	0.8	EtOH	0
7	**I**	**B**	0.9	H_2O	15
8	**II**	**B**	0.9	MeOH	0
9	**I**	**C**	0.8	H_2O	29
10	**I**	**C**	0.8	MeOH	62
11	**I**	**C**	0.9	EtOH	17
12	**II**	**C**	2.5	MeOH	37
13	**I**	**D1**	0.9	H_2O	100
14	**I**	**D2**	0.9	H_2O	100
15	**I**	**D2**	3.5	H_2O	100[c]
16	**I**	**D2**	0.9	H_2O	44[d] (82[d,e])
17	**II**	**D2**	3.2	MeOH	34
18	**II**	**D2**	3.2	EtOH	81

[a] Reaction time 4 h.
[b] Recycled catalyst.
[c] Yield 100, 100, 98, and 99% in the second, third, fourth, and fifth catalytic series, respectively.
[d] At room temperature.
[e] Reaction time 5 h.

Scheme 1.



I, II III, IV

I, **III**, R = H; **II**, **IV**, R = Et.

Initially, we tested Pd-containing catalysts on the basis of silica-supported chitosan: KSS silica gel no. 3, grain size 0.4–0.6 (**A1**) and 0.25–0.45 mm (**A2**). In both cases, the concentration of palladium in the catalyst was 0.05 wt %. Chitosan metal complexes are

immobilized on the silica surface to enlarge the catalyst surface and hence to increase accessibility of catalytically active centers. While studying the catalytic activity of palladium, copper, and cobalt-containing chitosan complexes in hydrogenation and oxidation processes, it was shown that three-component systems in which the metal–chitosan complex is immobilized on the surface of a wide-pore mineral support possess the highest efficiency [20–23].

Catalyst **A1** was found to be effective in the hydrogenation of phosphonic acid **I** in water: the reaction was complete in 1 h, yielding 1-phenylethylphosphonic acid (**III**) as the only product in the presence of less than 1 mol % of palladium (see table, run no. 1). Catalyst **A2** with smaller grains was less active: after 1 h, the conversion of acid **I** was 77%, and about 4 h was necessary to complete the process (run no. 2).

The rate of hydrogenation slightly decreases in going from water to methanol (cf. run nos. 1 and 3), and the reaction sharply slows down when ethanol is used as solvent: the yield of acid **III** in ethanol in the presence of catalyst **A2** was as low as 8% (run no. 4). These data may be rationalized taking into account the known solubility of chitosan in dilute acids [24]. Presumably, water and methanol (run nos. 1–3) promote appreciable removal of chitosan from the silica surface [removal of chitosan from finer catalyst **A2** occurs to a lesser extent (cf. run nos. 1 and 2)], so that the catalysis becomes essentially homogeneous. In fact, when catalyst **A1** was used repeatedly in methanol, the yield of **III** fell down from 94 to 30% (run no. 3). Ethanol poorly dissolves chitosan, and the heterogeneous catalyst shows a low activity (run no. 4). The same pattern was observed for neutral solutions of ester **II** in alcohols: the catalyst was inactive, and no hydrogenation of the substrate occurred (run nos. 5, 6).

It is known that modification of chitosan (as a rule, at the amino group) by treatment with various cross-linking agents increases its stability in acid medium [2, 25]. We have synthesized and tested two-component heterogeneous palladium catalysts on the basis of chitosan modified by α-ketoglutaric acid (catalyst **B**, palladium concentration 2 mol %) and glutaraldehyde (catalyst **C**, palladium concentration 1 wt %). Catalyst **B** turned out to be inactive in the hydrogenation of acid **I** (run no. 7) and ester **II** (run no. 8). Catalyst **C** was more effective (cf. run nos. 9 and 7, 12 and 8), but its application was complicated by appreciable formation of colloid systems: the reaction mixtures in run nos. 9 and 10 were clearly gel-like.

On the basis of glutaraldehyde-modified chitosan we prepared silica-supported metal complexes containing 0.05 (**D1**) and 1 mol % of palladium (**D2**). Both these three-component systems showed a high catalytic activity in the hydrogenation of acid **I** in water: the yield of **III** was 100% (run. nos. 13–15), and it almost did not decrease after repeated use of the catalyst (98–99% in the fourth and fifth catalytic series; run no. 15). The rate of hydrogenation was considerably lower at room temperature: the yield of acid **III** was 14% in 1 h, while it increased to 82% when the reaction time was prolonged to 5 h (run no. 16).

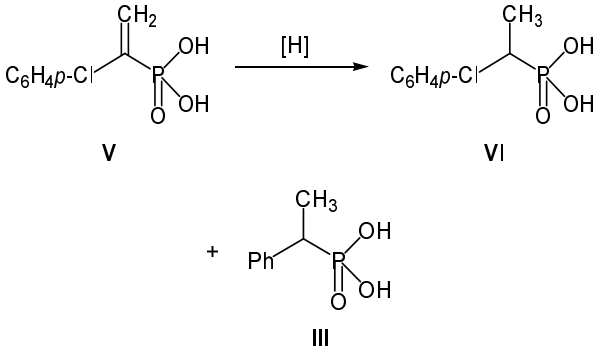
Catalyst **D2** also ensured hydrogenation of ester **II**; however, the reaction was slower than with acid **I**: even when the amount of the catalyst was increased to 3.2 mol %, the yield of saturated compound **IV** in 1 h reached 34 (run no. 17) or 81% (run. no. 18) in boiling methanol or ethanol, respectively. Water was not tested as solvent in the hydrogenation of ester **II** owing to its poor solubility.

Probable reasons for the observed differences in the catalytic activities of three-component systems **A1**/**A2** and **D1**/**D2** are specific morphologies and structures of the catalysts. This assumption was confirmed by the results of studying the surface of catalysts **A1** and **D2** by scanning electron microscopy (see figure). At a magnification of ×5000, we can clearly see a thin film with no breaks formed by the Pd–chitosan complex on the surface of **A1** particles; the film flows into pores of the support to form a uniform coating. In the case of catalyst **D2**, the metal–polymer complex on the silica surface forms a nonuniform crust-like coating rather than thin film. Photographs of **D2** samples obtained after the hydrogenation process show that the coating structure is conserved. Therefore, this catalyst almost does not lose its activity after 5 catalytic series (run no. 15).

With 1-(4-chlorophenyl)ethenylphosphonic acid (**V**) as substrate we estimated the possibility of using chitosan-based palladium catalsysts for chemoselective reduction of 1-arylethenylphosphonates having labile substituents in the aromatic ring. There are published data demonstrating successful application of chitosan–palladium complexes in both selective reduction of chlorine-containing substrates (e.g., chloronitrobenzene) without hydrodechlorination and reductive dechlorination (e.g., of chlorophenol) [5]. As we showed in [15], the reduction of acid **V** (δ_P 15.7 ppm, CD_3OD) with ammonium formate over Pd/C was accompanied by hydrodechlorination to give an approximately equi-

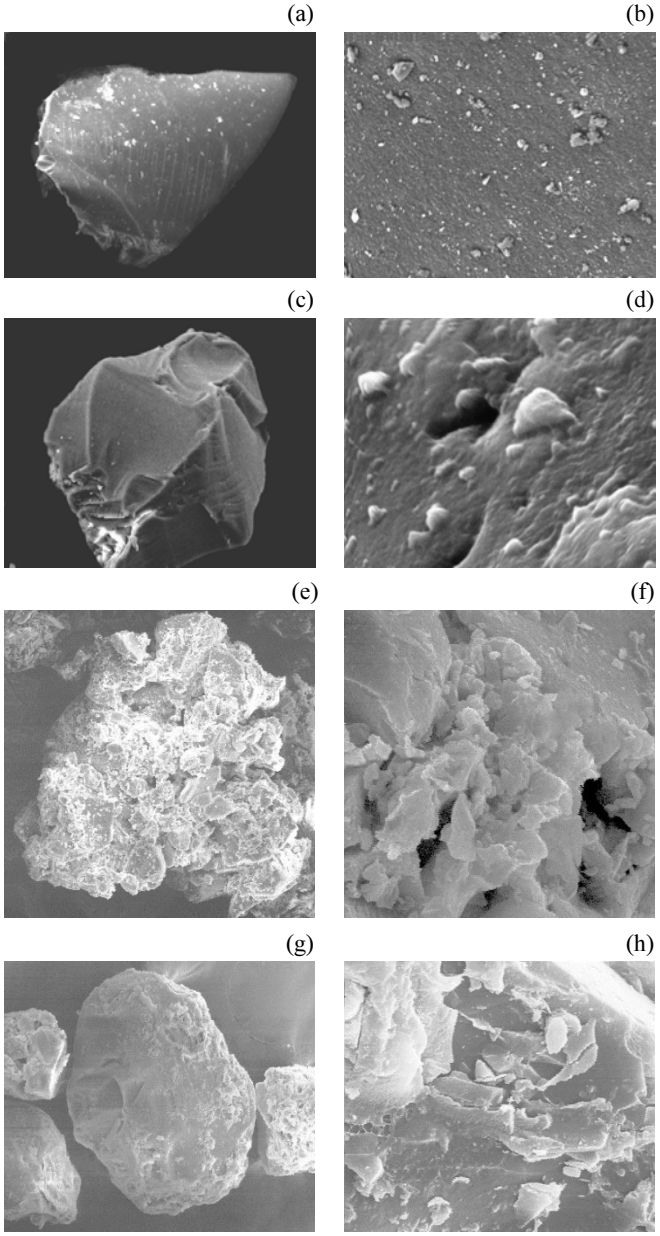
molar mixture of 1-(4-chlorophenyl)ethylphosphonic acid (**VI**; δ_P 29.3 ppm, CD_3OD) and 1-phenylethylphosphonic acid (**III**; δ_P 29.9 ppm, CD_3OD) (Scheme 2). An analogous pattern was observed in the electrochemical reduction of acid **V** at a palladated platinum electrode [26]. Modification of the electrode surface with cadmium considerably improved the selectivity for compound **VI**, but the conversion of initial acid **V** was not complete owing to self-inhibition. The yield of target acid **VI** was 59% at a conversion of 64% (maximally attainable) [27].

Scheme 2.



In the reduction of acid **V** with hydrogen in boiling water in the presence of **D2** the conversion was 94% in 1 h, and the yield of **VI** was 71%. This result allows us to anticipate that palladium complexes on the basis chitosan could ensure chemoselective hydrogenation of phosphonic acid **V**. Studies in this line will be continued.

We can conclude that three-component palladium-containing systems on the basis of chitosan applied onto the surface of wide-pore silica gel are active in the hydrogenation of 1-phenyletenhylphosphonic acid (**I**) and diethyl 1-phenylethenylphosphonate (**II**), as well as in the chemoselective hydrogenation of 1-(4-chlorophenyl)ethenylphosphonic acid (**V**). Studies by scanning electron microscopy showed formation of two kinds of supported catalysts: film and crust-like. The latter catalyst was obtained by modification of silica-supported chitosan with glutaraldehyde, and it can be used repeatedly without appreciable loss in catalytic activity.



Scanning electron microscopy photographs of the surfaces of silica and three-component catalysts: (a, b) silica particle, (c, d) **A1**, (e, f) **G2**, and (g, h) recycled **G2**; magnification (a, c, e, g) ×200 and (b, d, f, h) ×5000.

EXPERIMENTAL

The ^{31}P NMR spectra were recorded on a Bruker Avance-400 spectrometer (162 MHz); the chemical shifts were measured relative to 85% H_3PO_4. The catalyst surface was studied using a JSM-5300LV JEOL scanning microscope; samples were preliminarily coated with a thin layer of gold on a JFC-1100E setup.

Methanol was heated under reflux over magnesium methoxide and distilled. Ethanol was heated under reflux over calcium ethoxide and distilled. 1-Phenylethenylphosphonic acid (**I**), diethyl 1-phenylethenylphosphonate (**II**), and 1-(4-chlorophenyl)ethenylphosphonic acid (**V**) were synthesized as described in [15]. Chitosan isolated from crab shells (molecular weight

100000 to 150000, degree of deacetylation of amino groups 70%, water concentration 3 mol %; produced in Korea) was used.

Catalysts A1 and A2. Amorphous silica (KSS no. 3, grain size 0.4–0.6 or 0.25–0.45 mm, respectively; S_{BET} = 450 m^2/g; moisture capacity 1.4 ml/g), 1 g, was impregnated with 1.2 ml of a solution of palladium–chitosan complex prepared according to the procedure described in [22]. The impregnated sorbent was placed in a 0.5 M solution of NaOH for 15 min, filtered off, washed with several portions of distilled water until neutral washings, filtered off, and dried first for 24 h in air and then for 10 h under reduced pressure.

Catalysts B and C. Chitosan was modified with glutaraldehyde according to the procedures described in [25, 28, 29], and with α-oxoglutaric acid, as described in [30]. The modified polymers were treated with an aqueous solution of Na_2PdCl_4 (palladium concentration 1 wt % relative to the polymer). The mixture was stirred for 3 h, and the catalyst was filtered off, washed with several portions of distilled water, and dried for 24 h in air.

Catalyst D1 was prepared as described above for **A1** and **A2** from amorphous silica gel (KSK, 0.2–0.4 mm, S_{BET} = 450 m^2/g, moisture capacity 1.4 ml/g). Before treatment with alkali, the sorbent impregnated with the palladium–chitosan complex was treated with an aqueous solution of glutaraldehyde (calculated degree of cross-linking 12%). The concentration of palladium in the catalyst was 0.05 mol %.

Catalyst D2. Amorphous silica (KSK, 0.2–0.4 mm, S_{BET} = 450 m^2/g, moisture capacity 1.4 ml/g), 2 g, was impregnated with 3.0 ml of a solution of chitosan in 1% acetic acid. The impregnated sorbent was treated with 3.7 ml of an aqueous solution (50 vol %) of glutaraldehyde in 10 ml of methanol over a period of 1 h (calculated degree of cross-linking 10%). The sample was washed with methanol and dried in air. The above successive treatment of silica with chitosan and glutaraldehyde was repeated 3 times. The silica-supported chitosan thus obtained was treated with an aqueous solution of Na_2PdCl_4 (0.06 g in 15 ml of water). The sample was washed with water and methanol and dried in air. The concentration of palladium in the catalyst (2.210 g) was 1 wt % (0.022 g).

The completeness of palladium adsorption was checked by analyzing waste palladium solutions and washings by spectrophotometry. The concentration of palladium in the catalysts was also determined by atomic absorption spectroscopy. The prepared palladium complexes with chitosan and modified chitosans were characterized by IR Fourier spectroscopy and X-ray photoelectron spectroscopy; their spectral parameters coincided with those reported in [22].

Procedure for catalytic experiments. A flask equipped with a magnetic stirrer, reflux condenser with a Wurtz adapter, bubble counter, and a capillary passing through the reflux condenser to the bottom of the flask was charged with 0.24 mmol of appropriate substrate and 4 ml of a solvent. The flask was filled with argon through the capillary, and a specified amount of catalyst was added. Argon supply was terminated, and hydrogen was passed through the same capillary. The mixture was heated under reflux with stirring for a specified time in a continuous stream of hydrogen. It was then cooled, the catalyst was filtered off through a small layer of silica gel, the solvent was distilled off on a rotary evaporator, and the residue was dissolved in CD_3OD and analyzed by ^{31}P NMR spectroscopy.

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