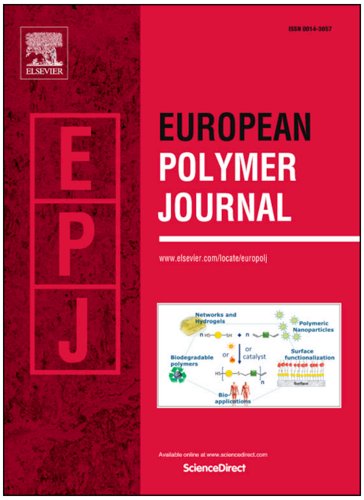

Combining polymer-bound catalyst with polymeric substrate for reproducible pH oscillations in palladium-catalysed oxidative carbonylation of alkynes

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Combining polymer-bound catalyst with polymeric substrate for reproducible pH oscillations in palladium-catalysed oxidative carbonylation of alkynes

Anna Isakova,*[1] George E. Parks,[2] Billy J. Murdoch,[3] Paul D. Topham,[2] Katarina Novakovic[1]

1. School of Engineering, Merz Court, Newcastle University, Newcastle upon Tyne, NE1 7RU;
2. Aston Institute for Materials Research, Aston University, Aston Triangle, Birmingham B4 7ET;
3. National EPSRC XPS Users' Service (NEXUS), School of Engineering, Newcastle University, Newcastle upon Tyne, NE1 7RU.

*Corresponding author: anna.isakova@newcastle.ac.uk.

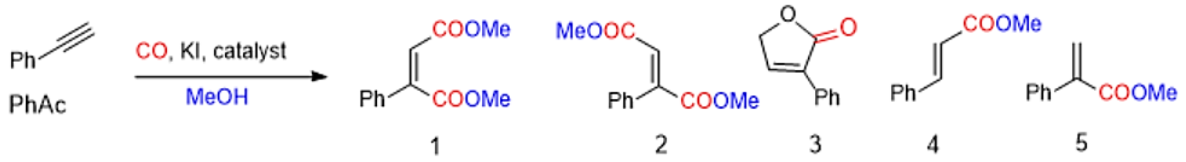
Abstract

Palladium-catalysed oxidative carbonylation (PCOC) of alkynes is a promising engine for building smart pulsatile polymeric systems, as it has demonstrated (in certain configurations) sustained regular oscillations in pH and redox potential for up to one month of monitoring in a batch reactor. Recent developments in polymer-supported palladium catalysts allowed to demonstrate the full capacity of this reaction - in a macrogel that experienced oscillations in volume, while releasing a drug load. In this work, we demonstrate reproducible oscillations (more than 100 h duration) in proline-functionalised chitosan-palladium system (Chi-Pro-Pd), using both small molecule (phenylacetylene) and polymeric (pegylated dialkyne) substrate, for the first time. Moreover, by functionalising chitosan with proline ligands, we dramatically reduced halide-mediated leaching of palladium, which readily occurred in non-functionalised chitosan-palladium catalysts (Chi-Pd). Oscillatory patterns for both systems confirm the need for fabricating functionalised chitosan supports to improve catalyst reusability and minimise loss of palladium.

Introduction

Oscillatory reactions are considered to be a powerful avenue for a smart self-pulsatile polymeric systems, if coupled to the right pH-, redox- or thermo-responsive polymer or hydrogel for a grand number of potential biomimetic applications [1–3]. Of the reported oscillatory reactions [4–8], palladium-catalysed oxidative carbonylation (PCOC) of alkynes (Scheme 1) is attracting attention as one of the most versatile reactions, capable of producing sustained (for up to one month of monitoring) oscillations in pH, redox potential, turbidity, and heater power (measured by power compensation calorimetry), where the amplitude and period can be successfully regulated by adjusting the reactant composition or temperature [9–16]. Moreover, PCOC readily proceeds in a batch reactor, whereas other similar oscillatory reactions coupled to smart materials generally proceed in continuous flow reactor conditions [17–19]. Donlon *et al.* have reported a polymeric substrate, alkyne-functionalised PEG (PEGA), as viable in oscillatory PCOC reaction, making this reaction system a good candidate for the fabrication of self-pulsatile materials [20]. While most of the earlier studies of PCOC were carried out using PdI_2 as catalyst, it was found that the solubility of PdI_2 in methanolic KI solution was one of the main factors that limited the reproducibility of the system [21], hence the need in expanding the library of palladium catalyst to more soluble (e.g., palladium acetate, which readily dissolves in methanolic KI solution [13]) or the opposite – polymeric catalysts that would not leach any palladium into solution.

Indeed, to efficiently catalyse PCOC in an all-polymeric system and be biocompatible for any potential biomimetic application, palladium catalyst has to be polymer-bound. Recently, we have demonstrated oscillations in a commercial phenyl phosphine-based polymeric palladium acetate catalyst (with 5% Pd content), however, oscillations were only triggered by addition of hydroiodic acid and had a mixed-mode nature (irregular) [13]. Furthermore, a reported issue with polymer bound Pd catalytic systems is its leaching from the polymer or clay matrix [22–24], especially in the presence of halide ions [25], affecting not only recyclability of the catalyst and the nature of catalysis (polymer bound heterogeneous catalysis becomes mixed heterogeneous-homogeneous due to leached Pd in solution), but its biocompatibility for potential applications. Since PCOC is carried out in a large excess of KI, it is necessary to make sure that chelation in Pd catalyst is strong enough to prevent Pd from escaping into the reaction solution.



Scheme 1. PCOC reaction, employing phenylacetylene (PhAc) as a substrate in KI/methanol, generating five mostly reported products: dimethyl 2-phenylmaleate (1), dimethyl 2-phenylfumarate (2), 3-phenyl-5H-furan-2-one (3), methyl cinnamate (4) and methyl atropate (5). The product distribution depends on the nature of catalyst, reaction conditions [13,26].

A great candidate for producing highly biocompatible pulsatile hydrogels is chitosan [27,28]. It is a biodegradable natural polymer with high chemical versatility [29–35]. Chitosan contains abundant -NH_2 and -OH groups that work as good chelators for Pd [36,37]. A number of examples of chitosan-based Pd polymers were reported that demonstrated no leaching, or minimal leaching, during the catalytic reaction [36,38–40]. Recently, we have reported an imine-functionalised palladium-bearing chitosan polymer as a viable catalyst in the PCOC system [3]. Importantly, we showed that hydrogels made from this Pd-polymer, chitosan and the crosslinking agent when used in PCOC reaction system yield sustained pH oscillations. No catalyst leaching was detected. Encouraged by these results, in this work, we have fabricated a proline-functionalised chitosan-palladium catalyst and compared its activity and leaching rates in an oscillatory PCOC reaction to chitosan simply impregnated with palladium, demonstrating that functionalisation of chitosan is necessary to produce stable and efficient palladium catalysts.

Experimental

Materials were used as received: palladium chloride (≥99.9%), chitosan medium molecular weight (75-85% deacetylated), L-proline (ReagentPlus®, ≥99% HPLC), N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDCI, crystalline), sodium chloride (ACS reagent, ≥99.0%), hydroiodic acid (≥57%), phenylacetylene (98%), methanol (HPLC Plus, ≥99.9), all Sigma Aldrich; naphthalene (extra pure), potassium iodide (≥99% GPR RECTAPUR®), all VWR Chemicals; buffer solutions: pH 2.00 (glycine), pH 7 (phosphate) and pH 10 (borate) (all NIST Standard, ready to use for pH measurement, Fisher Chemical). Dialkyne-functionalised poly(ethylene glycol) (PEGDAC) was synthesised according to previous reports from 2,000 g/mol PEG [41]. Pure air and carbon monoxide were supplied by BOC.

Synthesis of proline-functionalised chitosan-palladium catalyst: 0.5 g of chitosan (particles of 0.5-2 mm size, as supplied by SA), 450 mg of proline hydrochloride and 1200 mg of EDCI were suspended in 30 ml of methanol. Then 10 ml of water (adjusted to pH 4 by HCl) was added while stirring. The reaction mixture was allowed to stir overnight, then filtered, the solids washed with methanol, collected and dried in vacuo, resulting in dark brown chitosan particles (Chi-Pro, 586 mg). Chi-Pro-Pd was stirred with 1 mg/mL K_2PdCl_4 in methanol for 24 h, filtered and washed with methanol to remove any unreacted K_2PdCl_4. The solids were collected, dried in vacuo, resulting in dark black particles (Chi-Pro-Pd, 635 mg).

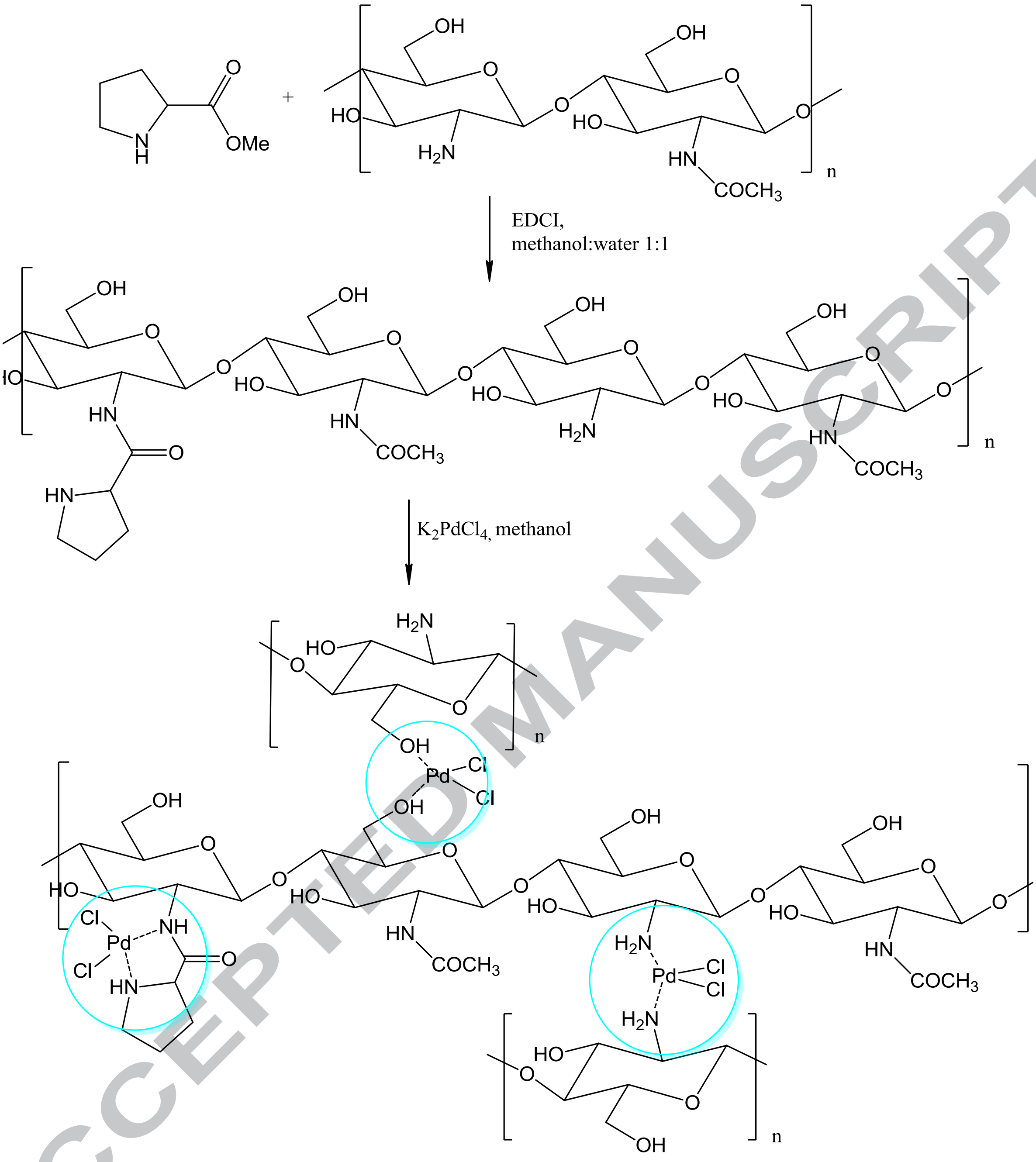
Synthesis of chitosan impregnated with palladium: 0.5 g of chitosan was stirred with 1 mg/mL K_2PdCl_4 in methanol for 24 h, filtered and washed with methanol to remove any unreacted K_2PdCl_4. The solids were collected, dried *in vacuo*, resulting in brown particles (Chi-Pd, 524 mg).

PCOC reaction was performed at approximately 20 °C in a flat-bottom Erlenmeyer flask (100 mL) at constant stirring, using HEL micronote system to log pH and temperature within the bulk of the reaction. Prior the reaction, pH probe was calibrated at room temperature against NIST-traceabale buffer solutions of pH 2, 7 and 10. 4.150 g of KI, 200 mg of Chi-Pro-Pd or Chi-Pd catalyst and 256 mg of naphthalene (internal standard) were all charged into the flask in their solid state and suspended in 100 mL HPLC grade methanol by stirring. The pH and temperature monitoring started while KI was dissolving and continued throughout the experiment. Stabilisation of pH indicated that the dissolution of KI was complete. Then, the CO and air purging through the solution at flow rate of 15 mL/min each commenced. After initial pH drop, value stabilised, and the 1.38 mL (12.57 mmol) of phenylacetylene or 130 mg of PEGDAC was added. The pH and temperature were monitored for at least 6000 min. It should be noted that presented system was monitored in methanol, whereas the pH calibration was performed using aqueous buffer solutions. Since the standard pH scale is based on aqueous measurements, if pH values reported in this study are to be converted to hydrogen ion concentrations the recorded values would need to be adjusted to reflect methanol environment. It has been reported that to get an equivalent in aqueous solutions, the pH values obtained in methanol can be adjusted by adding 2.3 pH units [42].

X-ray Photoelectron Spectroscopy (XPS) was performed on solid catalysts in a Thermo Scientific K-Alpha spectrometer using a monochromated Al K-Alpha source (1486 eV). The flood gun was used for charge compensation.

Thermogravimetric analysis (TGA) was performed on Pyris 1 TGA instrument under nitrogen atmosphere with a heating rate of 10 °C min^{-1}.

Results and Discussion



Scheme 2. Synthesis of Chi-Pro-Pd. Potential binding sites for Pd are labelled with blue circles.

Proline-functionalised chitosan was synthesised using a standard EDCIcoupling approach (Scheme 2) [40]. Success of the synthesis was confirmed by FTIR, where the relative change of intensity of the amide band at 1640 cm^{-1} increased due to the formation of additional amide bonds (Figure 1a) and the intensity of the C-N amino bands at 1380, 1300 and 1080 cm^{-1} has decreased. Subsequently, proline-functionalised chitosan was stirred with K_2PdCl_4 in methanol to yield Chi-Pro-Pd catalyst. It is important to note that chitosan has multiple binding ligands for Pd even prior to functionalisation, and since Pd requires bidentate binding, it may utilise ligands on different chitosan chains, thus crosslinking them. After functionalisation, Chi-Pro-Pd becomes insoluble in 1% acetic acid (good solvent). To estimate the intrinsic ability of chitosan polymer to bind palladium and form stable structures, we stirred untreated chitosan with K_2PdCl_4 to obtain Chi-Pd, as a reference material.

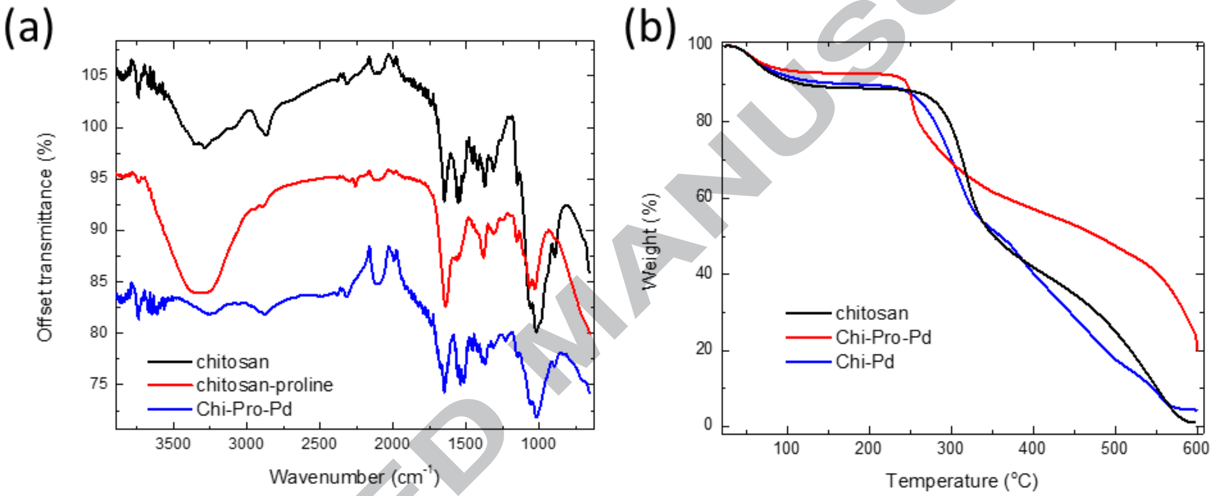


Figure 1. (a) FTIR spectra of chitosan (black), proline-functionalised polymer (red) and Chi-Pro-Pd (blue). (b) TGA thermograms of pristine chitosan (black), Chi-Pro-Pd (red) and Chi-Pd (blue).

According to inductively coupled plasma optical emission spectrometry (ICP-OES), used to estimate Pd content in both polymer catalysts, the content of Pd in Chi-Pro-Pd was 6.85 wt% and in Chi-Pd 2.5%. On the other hand, TGA (Figure 1b) performed up to 600 °C showed that Chi-Pro-Pd had 20.3% of char and Chi-Pd 4.3% of char at the end of the run, whereas pure chitosan left 1.31% of char, which is within the acceptable limits for the entirely organic polymer. Moreover, pure chitosan and Chi-Pd had very similar thermal degradation profiles, indicating that the bonds between Pd and chitosan were not strong enough to affect the thermodynamics of bond breaking. At the same time, Chi-Pro-Pd polymer demonstrated an earlier onset of thermal degradation at 223 °C.

The disagreement between two measurements is associated with the fact that the TGA is relying on the assumption that all char (apart from 1.31%) was of inorganic (Pd) matter. In this case, however, thermal degradation of the Pd-containing samples was retarded and full degradation of Chi-Pro-Pd would occur at much higher temperatures due to the bonds of the organic part of the catalyst to palladium. Generally, in both measurements, Chi-Pro-Pd demonstrated higher binding capacity for Pd, arising from the functionalised proline ligands.

In order to understand the chemical state of palladium within the chitosan-based catalysts and the coordination of macromolecular ligands with metal ions, the binding energies of Pd were obtained by X-ray photoelectron spectroscopy (XPS). The binding energies of Pd 3d 5/2 in both catalysts are similar (335.3 eV) which suggests that Pd^{2+} has converted into Pd^0 during synthesis. The binding energy of N 1s in Chi-Pro-Pd and Chi-Pd is higher than in Chi-Pro and Chi (Table 1) which indicates that the lone-pair of electrons on the nitrogen delocalises over to Pd atom and the electron cloud density at the nitrogen atom decreases [43]. The binding energy of O 1s in Chi-Pro-Pd and Chi-Pd also increased, indicating that oxygen in the polymer ligand also participates in binding of palladium.

Table 1. Binding energies (in eV) of Pd, O and N in chitosan derivatives containing palladium.

	Pd3d5/2	**O 1s**	**N1s**
Chi-Pro	-	531.8	398.9
Chi-Pro-Pd	335.3	532.3	399.5
Chi	-	531.8	398.6
Chi-Pd	335.3	532.3	399.2

Both catalysts were employed in a PCOC reaction using phenylacetylene as substrate and pH was recorded. As can be seen in Figure 2, both catalysts were able to successfully catalyse the reaction and generate oscillations in pH. However, the pattern of oscillations was dramatically different. In Chi-Pro-Pd (Figure 2a), oscillations started 190 min after addition of substrate, having a period of 49-69 min and an amplitude gradually varying between 0.2 and 1.82 pH units. The shape of each oscillation is very similar to that typically observed in PCOC reactions employing small molecule palladium acetate and palladium iodide catalysts [13,26]. In Chi-Pd (Figure 2b), the fall in pH associated with addition of substrate was followed by a rapid recovery of pH, following which the oscillations started in 195 min, similar to Chi-Pro-Pd. The oscillations for Chi-Pd had an irregular step-like pattern, where the period of oscillations increased from 154 min to 958 min and the amplitude – from 0.37 to 0.9 pH units. Moreover, the shape of oscillations was indicative of two processes with different rates occurring in the reaction, in this case – simultaneous heterogeneous and homogeneous catalysis.

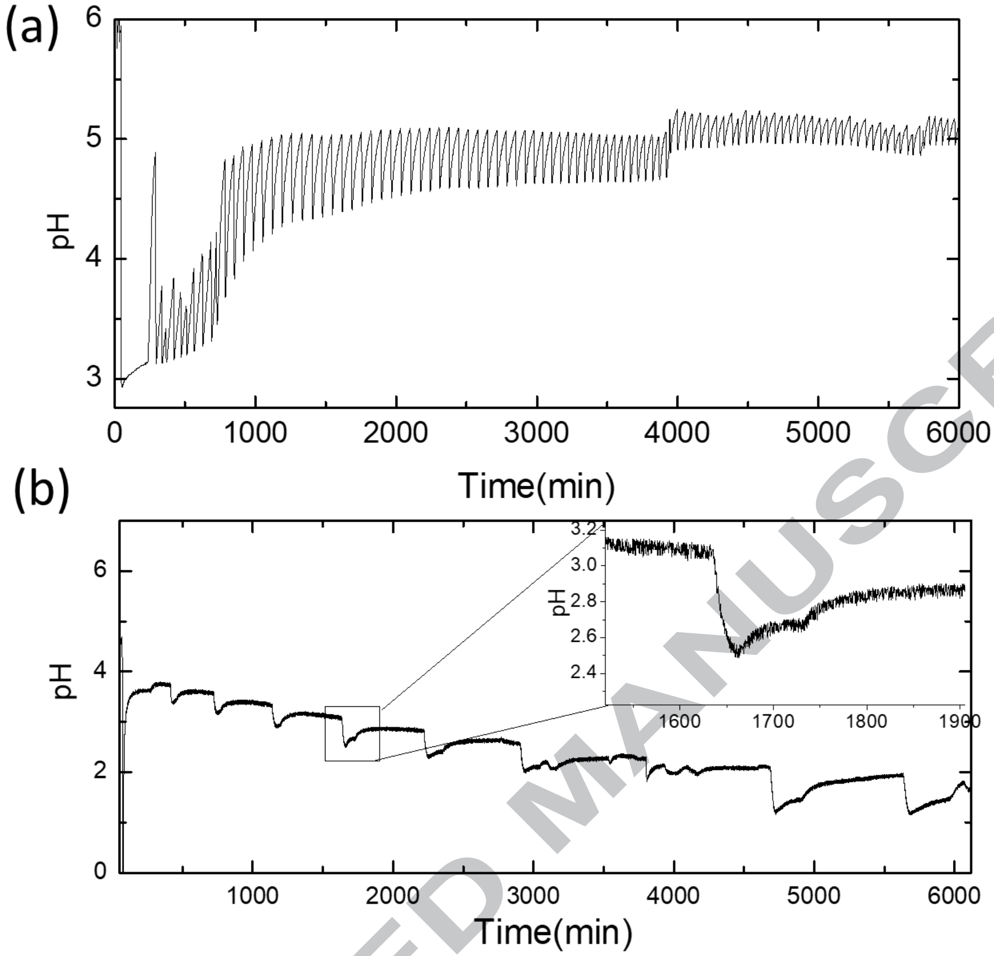


Figure 2. pH traces of (a) Chi-Pro-Pd and (b) Chi-Pd catalysed carbonylation reaction using phenylacetylene as a substrate. Inset shows pH evolution within one oscillation in the Chi-Pd-catalysed system where two processes with different rates are observed.

After 7000 min, the conversion of starting material in Chi-Pro-Pd was only 9.41% (as measured by GC-MS), compared to that of 69.98% in Chi-Pd catalytic system. Although the oscillations were much more pronounced and regular in Chi-Pro-Pd system, the conversion is low which is reminiscent of catalysis in palladium acetate reactions where oscillations are observed at pH 3-4 (methanol solution). In Chi-Pd system, however, the reaction occurs mostly at lower pH levels (higher concentrations of H^+ ions) and thus provides greater conversion. Observed trends suggest that Chi-Pro-Pd catalysis proceeds in a slower manner as the catalyst remains heterogenous, bound to the polymer structure, and the reaction requires liquid to solid diffusion, reaction on the solid surface and subsequent diffusion back into the liquid phase. On the other hand, higher conversions and lower pH recorded for Chi-Pd suggest catalyst leaching and a homogeneous PdI_2 (from leached Pd) catalytic path [21,26,44].

The same catalysts were employed in a PCOC reaction using polymeric dialkyne-functionalised PEG polymer – PEGDAC [1]. In the Chi-Pro-Pd catalysed reaction (Figure 3a), the addition of substrate did not lead to an immediate pH drop, instead the pH increased marginally and after 10 min experienced a sudden drop from 7.5 to 5.8, from where it recovered to pH 6.45. At 750 min, a series of 'cascade' oscillations was observed, gradually decreasing in amplitude from 4.12 pH units to ~ 1, with a period dropping from 87 min to 66 min. After the first series of oscillations, the next pH drop only occurred at 2440 min. The second series of oscillations had a much smaller amplitude and longer periods that tended to get shorter – from 1480 min to 604 min. When the same catalyst was recycled under the same conditions in a fresh reaction batch (Figure 3b), the oscillation pattern was preserved (i.e. first a single pH drop and recovery, then a series of large oscillations, followed by smaller oscillations at longer periods), however, the time scales were much shorter. Thus, in recycled Chi-Pro-Pd, the first series of oscillations started at 225 min and was complete by 700 min, whereas in fresh catalyst these oscillations only started at 750 min and continued for another 750 min. Additionally, the later oscillations were more pronounced and reached amplitudes of 1.25-1.60 pH units.

With fresh Chi-Pd catalyst, the system demonstrated a different behaviour (Figure 3c). After addition of substrate, a pronounced pH drop was observed from 5 to 1.65, which then slowly recovered. Oscillations were observed during this recovery, with a varying amplitude and period and were finished by 500 min. After this time, the oscillations were no longer observed. With recycled Chi-Pd, this pattern was not observed (Figure 3d). Upon addition of substrate, a significant drop of pH from 7.5 to 3.85 occurred, which then slightly recovered to 4.6. Small oscillations in pH were observed at pH 4.6-4.7 with an amplitude of 0.06 pH units and a period of 30-40 min, which rapidly disappeared after 500 min. It is possible that their amplitude decreased after 500 min to below the levels of instrumental resolution. Further, during the experimental run, the oscillations seemed to reappear.

Clearly, recycling the Chi-Pd catalyst led to almost absolute loss of catalytic activity, associated with leaching of palladium into the reaction media. Indeed, ICP –OES analysis has shown that only 0.4% Pd is retained in the Chi-Pd catalyst after the first PEGDAC run, whereas Chi-Pro-Pd demonstrated only 0.45% loss, retaining 6.4% of Pd. The loss of palladium in Chi-Pro-Pd was associated mainly with Pd escaping from pristine chitosan moieties, while the metal bound to the proline ligand remained.

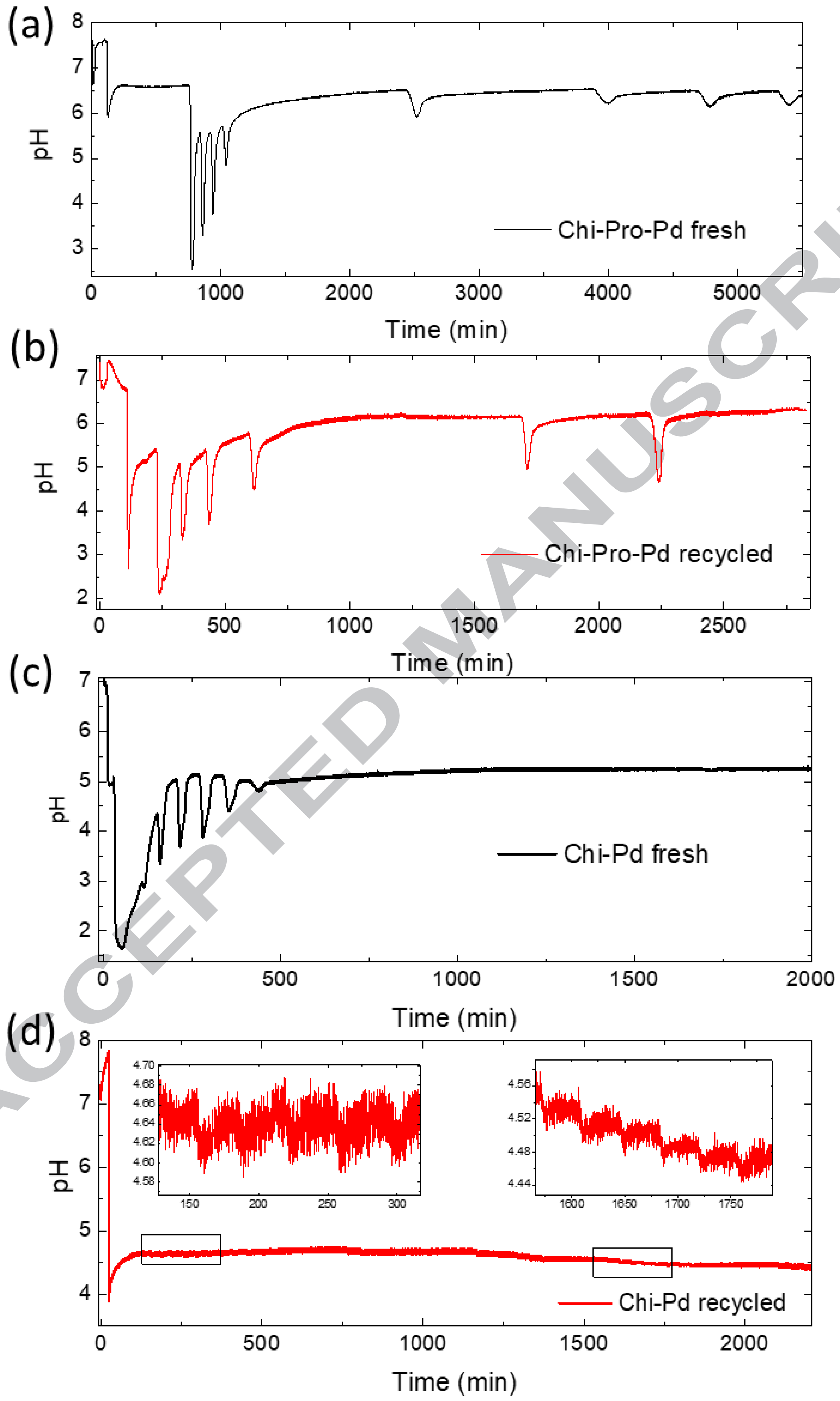

(a)
pH
8
7
6
5
4
3
0
1000
2000
3000
4000
5000
Time (min)
Chi-Pro-Pd fresh
(b)
pH
7
6
5
4
3
2
0
500
1000
1500
2000
2500
Time (min)
Chi-Pro-Pd recycled
(c)
pH
7
6
5
4
3
2
0
500
1000
1500
2000
Time (min)
Chi-Pd fresh
(d)
pH
8
7
6
5
4
4.70
4.68
4.66
4.64
4.62
4.60
4.58
150
200
250
300
4.56
4.52
4.48
4.44
1600
1650
1700
1750
0
500
1000
1500
2000
Time (min)
Chi-Pd recycled

Figure 3. pH traces of Chi-Pro-Pd (a, fresh and b, recycled) and Chi-Pd (c, fresh and d, recycled) catalysed carbonylation reactions using PEGDAC as a substrate.

Indeed, the pH pattern of the Chi-Pd-catalysed reaction had significant similarities with the $PdCl_2$ –catalysed run (Figure 4). In the $PdCl_2$ run, the addition of PEGDAC substrate led to a drop of pH from 5.03 to 1.85, after which the pH recovered while producing oscillations. These oscillations started with a smaller amplitude and period than those, produced by Chi-Pd, but had a similar pattern. In total, the oscillations in $PdCl_2$-catalysed reaction lasted for 2000 min (black line in Fig. 4) before pH stabilised at 4.6, indicating that the substrate was almost fully consumed.

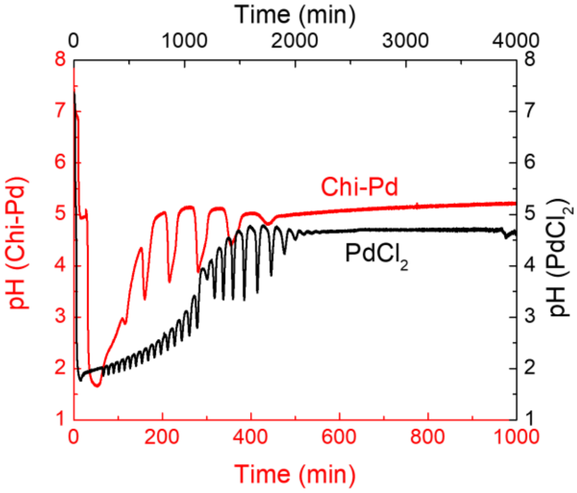


Figure 4. pH oscillations in $PdCl_2$ (black) and Chi-Pd catalysed PCOC (red), employing PEGDAC substrate.

These data suggest that the oscillation pattern in Chi-Pd was mostly dictated by leached palladium, and thus by homogeneous catalysis, whereas in Chi-Pro-Pd system, most of Pd remained bound to the polymer, and thus heterogeneous catalysis generated the observed specific oscillatory pattern. These findings show that Chi-Pro-Pd system has a potential for future use in various applications where palladium leaching has to be minimised, after a preliminary washing with saturated KI solution to remove any Pd that is bound to chitosan directly (through weak bonding). Moreover, these findings confirm that all future polymer-Pd catalytic systems designated for oscillatory reactions should rely on strong ligands for binding of palladium to help avoid any halide-induced leaching of palladium into solution and generation of homogeneous catalytic pathway alongside the heterogeneous pathway.

Conclusions

We report an oscillatory regime of proline-functionalised chitosan-palladium catalyst (Chi-Pro-Pd) in a palladium-catalysed carbonylation reaction, employing both small molecule and polymeric substrates. Although chitosan itself is capable of binding palladium, under the reaction conditions, non-functionalised chitosan-palladium was shown to rapidly leach palladium into the reaction media, rendering the catalyst non-reusable. At the same time, the Chi-Pro-Pd polymer was capable of generating oscillations of a similar pattern after recycling in a second run as a result of the preservation of the Pd content in the polymer. This is an important finding that supports further developments of all-polymeric oscillatory materials fit for a broad range of applications, including applications in medicine due to reduced toxicity of the catalyst. The successful recycling of Chi-Pro-Pd catalyst suggests that in prospective applications it will be possible to recharge the system by adding extra substrate, while reusing the same catalyst.

Conflicts of interest

No conflicts of interest to declare.

Acknowledgements

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Data availability

The raw/processed data required to reproduce these findings cannot be shared at this time due to legal or ethical reasons.

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Combining polymer-bound catalyst with polymeric substrate for reproducible pH oscillations in palladium-catalysed oxidative carbonylation of alkynes

Anna Isakova,[1] George E. Parks,[2] Billy J. Murdoch,[3] Paul D. Topham,[2] Katarina Novakovic[1]

4. School of Engineering, Merz Court, Newcastle University, Newcastle upon Tyne, NE1 7RU;
5. Aston Institute for Materials Research, Aston University, Aston Triangle, Birmingham B4 7ET;
6. National EPSRC XPS Users' Service (NEXUS), School of Engineering, Newcastle University, Newcastle upon Tyne, NE1 7RU.

Highlights

- pH oscillations in proline-chitosan-palladium catalyst, using phenylacetylene as a substrate;
- pH oscillations, using polymeric (pegylated dialkyne, PEGDA) substrate;
- Minimised leaching of palladium in proline-functionalised chitosan, compared to pristine;
- Reproducible pH oscillations of the original pattern generated by recycled catalyst.

Graphical abstract