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Polymers

Polydopamine—An Organocatalyst Rather than an Innocent Polymer

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Dedicated to Professor Dr. Johann Mulzer on the occasion of his 70th birthday

Abstract: Polydopamine (PDA) is easily available by oxidation of dopamine and is widely used for persistent coatings of various materials. It is hitherto considered to be inert in many interesting biomedical and other applications. Results presented here, reveal an unexpected behavior of polydopamine as an organocatalyst in direct aldol reactions under mild conditions. Evidence was found for dual catalysis making use of amino and phenolic hydroxy groups found in PDA. Thus scientists must be aware that PDA is not an innocent polymer and can cause unwanted side effects in important applications, such as in biomedicine or as supports in catalysis.

Introduction

Phenolic motives in adhesive proteins containing DOPA enable mussels to fix themselves at almost each surface.[1–2] Chemists took lessons from this and found out that polydopamine (PDA) can also form resistant films on a variety of materials, such as metals, metaloxides, silica, glass, and polymers.[3–7] PDA coatings are considered to be nonpoisonous and biocompatible and have found various biomedical applications, such as in drug transport and delivery, as antibacterial coatings,[8–15] in separation of biological materials or poisonous contaminants,[16–17] and as supports for organocatalytic moieties.[18] PDA is a polymer formed by oxidation of dopamine. Although its structure is still under discussion, there is a consensus that it is built up of indole units of different states of hydrogenation, mainly connected by C–C bonds between the benzene rings.[19–20] Due to the presence of two oxygen atoms connected to the benzene ring, tautomerism of quinoid and catechol units is possible in appropriate substructures. In addition to indole units, evidence was found that PDA also contains dopamine units in the polymer backbone that are not cyclized, that is, they contain aminoethyl side chains.[19] So far, PDA is considered as a robust, relatively inert, and innocent coating material. On the other hand, PDA coatings also served as a medium for fixing various biomolecules or enzymes.[5,21–24] Here, the occurrence of carbonyl and Michael-acceptor moieties in PDA is exploited enabling reactions with amines or thiols as nucleophiles. Furthermore it is known that PDA can partially be hydrolyzed giving rise to the formation of carboxylic acid groups by opening the catechol ring.[25–26] Reactions of PDA with dimethyl sulfate or benzoyl chlorides as strong electrophiles were reported attacking nucleophilic sites such as amino or phenolic hydroxyl groups.[26] Finally the catechol/o-quinone moieties found in PDA provide redox properties, which can be exploited in reduction and deposition of metals, such as Au, Cu, or Ag.[15,27–29] We disclose here that, surprisingly, PDA and PDA-coated magnetic nanoparticles exhibit organocatalytic properties in aldol reactions under mild conditions thus revealing that PDA is not an innocent polymer as is often assumed. This observation is of great importance in fields in which PDA is used as coatings for materials applied in biology, medicine, and catalysis where it is assumed to be inert.

Results and Discussion

We recently developed PDA-covered magnetite nanoparticles (MNP) equipped with azido groups that are useful attachment points for other functions with help of copper-catalyzed azide alkyne cycloaddition (CuAAC), the most important of the click reactions, by 1,2,3-triazole formation.[18] In this way it was possible to link biotin as a biological recognition function, dansyl as a fluorescence marker, and (*S*)-proline as an organocatalyst to PDA-coated MNP. In the further course of our work, we tested the behavior of these proline-containing nanoparticles as magnetically supported organocatalysts. The fixation of the organocatalytic unit to MNP provides easy separation of the organocatalyst by magnetic decantation and is in the focus of contemporary research.[30–33] Application of the proline-functionalized MNP as a catalyst in asymmetric direct aldol reactions revealed the formation of the expected aldol product;

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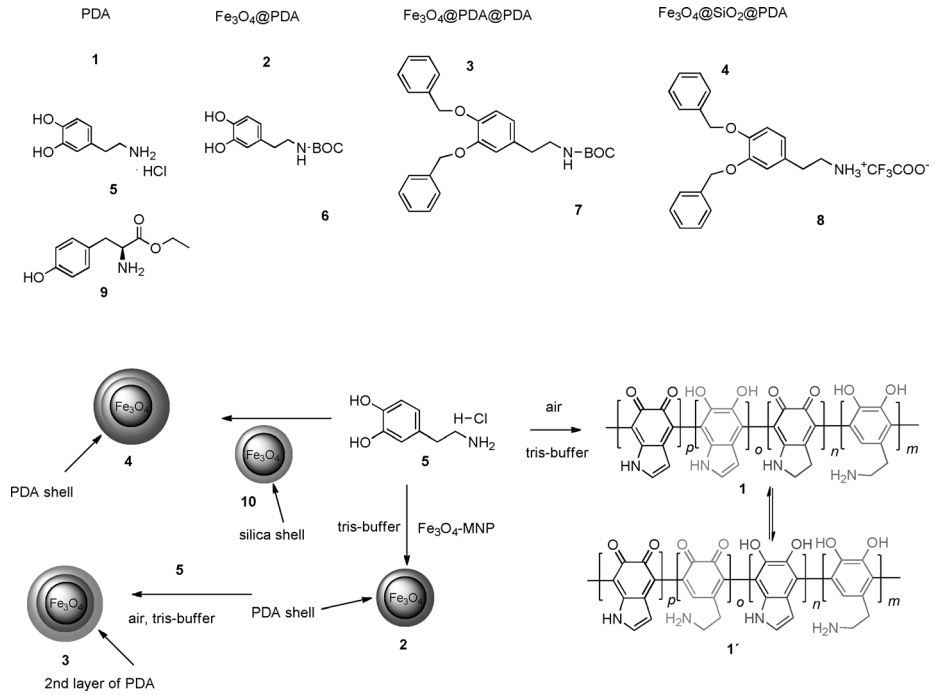


Scheme 1. Synthesis of PDA and PDA-coated MNP.

however, as a racemate. Considering the fact that other 4-hydroxyproline derivatives led to excellent enantioselectivities,[34] the question appeared as to why our catalyst failed in this respect. A nonstereoselective background reaction catalyzed by the PDA coating could explain this phenomenon.

To find out if this supposition was justified, we checked PDA **1** and MNP–PDA **2** and **3** in this respect. To exclude eventual background catalysis by the magnetite support also MNP **10** protected with a silica shell were included as magnetic supports for PDA leading to MNP **4**. The PDA-covered MNP **2**, **3**, and **4** were obtained as depicted in Scheme 1 by oxidative polymerization of dopamine in tris-buffer as the most often used method[3] in the presence of the respective nanoparticles. In addition to MNP **2**–**4** different monomer derivatives **5**–**9**, which may be important motifs for the catalytic activity of PDA, were also tested.

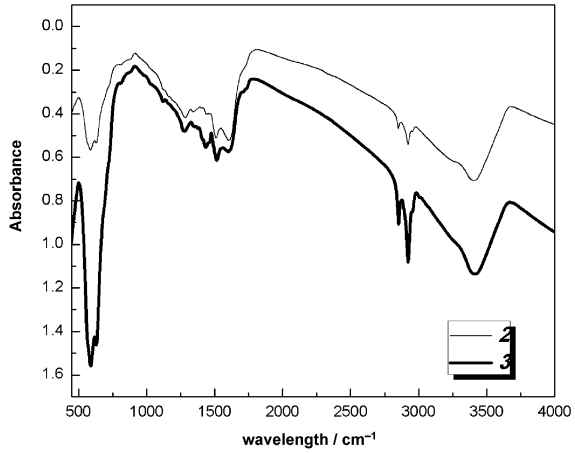


Figure 1. FTIR spectra of MNP **2** and **3**.

Before applying the PDA-coated MNP (**2**, **3**, and **4**) in catalytic tests they were characterized by FTIR spectroscopy (typical peaks for PDA at 1440–1620 cm^{-1}) (Figures 1 and 2). TEM investigations showed an almost spherical shape for MNP **3** and **4** (see the Supporting Information, Figures S1–S3). All the MNP **2**–**4** and **10** exhibited superparamagnetic behavior with good saturation magnetization values of 47.7 (**2**), 32.3 (**3**), 36.6 (**4**), and 48.4 emu g^{-1} (**10**), which is important for their magnetic separation from reaction mixtures later on (Figures 3 and 4). In addition, AFM of PDA **1** is found in the Supporting Information (see the Supporting Information, Figure S9) and XPS in refer-

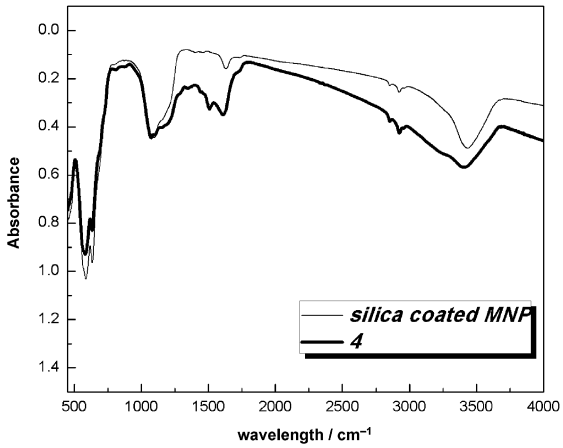


Figure 2. FTIR spectra of MNP **4** and silica-coated MNP **10**.

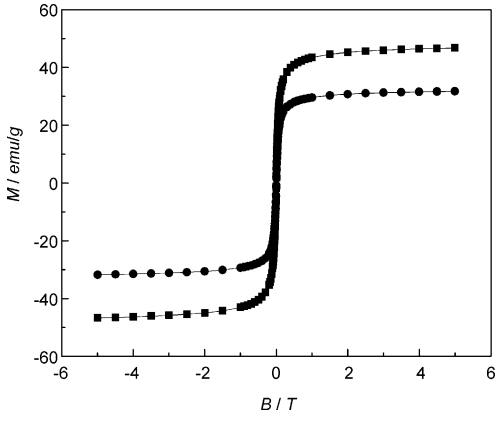


Figure 3. Magnetization vs. applied magnetic field dependences at room temperature of MNPs **2** and **3** (■: **2**; ●: **3**)

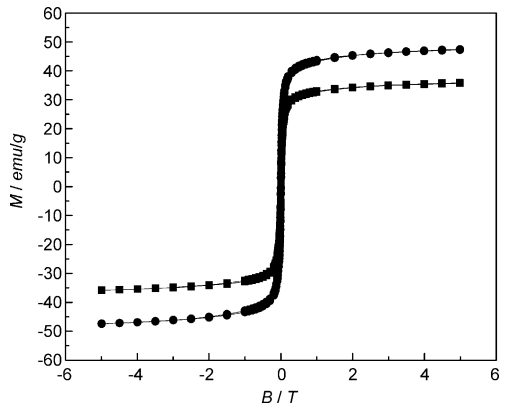


Figure 4. Magnetization vs. applied magnetic field dependences at room temperature of MNP **4** (■) and silica-coated MNP **10** (●).

ence [19]. PDA-coated magnetite nanoparticles **2** were characterized earlier by XPS. TGA of nanoparticles **2** (see ref [35]), **3** (see the Supporting Information, Figure S7), and **4** (see the Supporting Information, Figure S8) revealed 19.8, 34, and 19% organic material, respectively.

The direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone served as a test reaction for the presumed catalyst candidates **1**–**9** (Scheme 1, Table 1). It was performed at 50 °C by using an excess of cyclohexanone as the solvent. Remarkably, the application of mere PDA **1** gave rise to the formation of the aldol product **12** in 90% yield (Table 1, entry 3). Formation of the aldol product was only observed if additionally catalytic amounts of water were applied (compare entry 1 with entries 2–4). To find out if some change of PDA **1** occurred when it served as a catalyst in the aldol reaction it was separated from the reaction mixture by centrifugation and reused. Interestingly, the yield of aldol product dropped after first recycling (entry 5) but remained more or less constant in the subsequent three runs (entries 6–8). Obviously, some change occurred when PDA (**1**) was used in the first run resulting in a decrease of the catalytic performance. The resulting PDA still contained catalytic units, which were not affected later on when the catalyst was used again. To check if possibly a change in pH caused by PDA were responsible for the catalysis of the aldol reaction, the following experiments were performed: addition of PDA **1** to distilled water caused a change in the pH from 5.5 to 5.7, which is too small to catalyze the aldol reaction. On the other hand treatment of cyclohexanone with 4-nitrobenzaldehyde in water or phosphate buffer gave rise to the formation of the aldol product **12a** in 64 or 90% yield, respectively (entries 9 and 10). These results demonstrate that first the aldol reaction is catalyzed by the involvement of PDA and not by a simple change in pH and second that the catalytic activity of PDA is likely to occur also under biological conditions. In further experiments, PDA-coated magnetite nanoparticles **2** were investigated in direct aldol reactions (entries 11–13). Again, catalytic activity was observed leading to the aldol product **12** in 86% yield under optimized conditions (entry 12). The system **2** represents a magnetically supported organocatalyst and thus can be recovered by straightforward magnetic decantation. As in the case of nonsupported PDA **1** (entry 5), the yield of the aldol product dropped after recycling of **2** (entries 12 and 13). To compensate possible loss of catalytic PDA units from the surface of the nanoparticles in the case of **2**, the Fe_3O_4@PDA **2** nanoparticles were covered with a second shell of PDA to give particles **3** (Scheme 1). However, their application in the aldol reaction showed similar results. The yield dropped from originally 97 (entry 14) to 70% in the second run (entry 15). Surprisingly, the reaction resulted in as little as 13% yield in the third run (entry 16), a phenomenon which is difficult to understand.

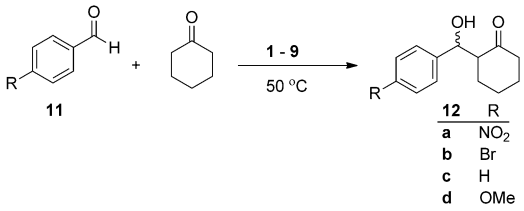
As another interesting issue, the diastereoselectivity of the aldol model reaction has to be discussed. With dopamine **1** the d.r. was close to 1:1 (Table 1, entries 1–8) while somewhat higher values were observed with the magnetite-supported PDA NP **2** (entries 11–13). In the case of magnetite NP **3** with a double layer of PDA the situation (entries 14, 15) is similar to mere PDA **1** but the d.r. increased from 55:45 (entry 14) to 70:30 after two recycling steps (entry 16).

Coverage of magnetite NP with silica prior to coating with PDA (MNP **4**) revealed a similar effect in the aldol reaction. A sharp drop of yield was observed after the first run from 75 to 40% (Table 1, entries 20, 21). To exclude that a shortage of water for hydrolytic cleavage of intermediates from the catalytic sites of PDA was responsible for such drops in yield, the aldol reaction was performed in water. However, the product was only formed in traces (entry 22) as also observed when **3** was used as the catalyst in water (not shown).

Magnetite PDA nanoparticles **3** were further tested in reactions with other arylaldehydes (entries 28–30). Whereas 4-bromobenzaldehyde gave a modest 48% yield of the aldol product (entry 28), benzaldehyde and anisaldehyde failed (entries 29 and 30). The fact that arylaldehydes lacking electron-withdrawing groups are less prone to aldol reactions observed here is a known phenomenon in organocatalyzed aldol reactions.[36]

To get more information on what structural elements in PDA might be responsible for the altogether unexpected and hitherto unknown behavior as an organocatalyst, also dopamine **5** and its derivatives **6**, **7**, and **8** were applied in direct aldol reactions. Application of dopamine hydrochloride **5** furnished the aldol product **12a** in 80% yield (Table 1, entry 23). If the amino group was blocked by *tert*-butoxycarbonyl (Boc) the reaction failed, like in the case of **7** wherein both the amino group and the hydroxyl groups were protected. On the other hand, a modest catalytic activity (25% yield) was observed with *O*,*O*-dibenzyldopamine (**8**) in which only the phenolic OH groups of dopamine were blocked. Taking these facts into consideration it seems that dopamine and probably also PDA react as dual catalysts wherein the amino group acts as an imine/enamine-forming organocatalytic unit while the acidic phenolic hydroxyl groups assist catalysis by H-bonding with carbonyl O-atoms (Scheme 2). In fact, enhancement of the catalytic performance of (*S*)-proline in aldol reactions by adding catalytic amounts of catechol was observed before.[37–38] As can be seen by the result obtained with tyrosine methyl ester **9** (entry 27) providing the aldol product in

Table 1. Direct aldol reaction of arylaldehydes **11** with cyclohexanone.



12	R
a	NO_2
b	Br
c	H
d	OMe

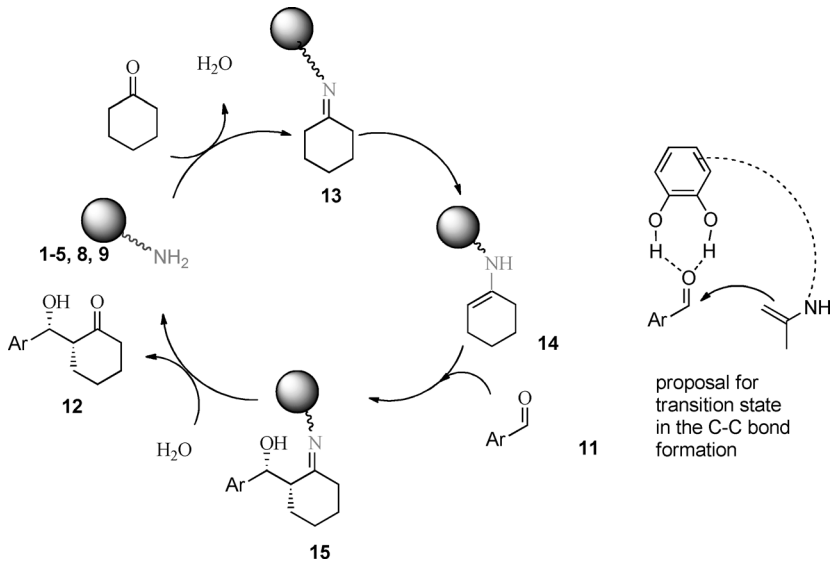
Entry[a]	Product **12**	Cat.	Amount [mg]	*t* [h]	Yield [%]	d.r. *syn*/anti
1	**a**	**1**[b]	100	24	trace	n.d.
2	**a**	**1**	50	8.5	65	56:44
3	**a**	**1**	100	5.5	90	57:43
4	**a**	**1** (1st run)	100	24	93	56:44
5	**a**	**1** (2nd run)	115	24	75	48:52
6	**a**	**1** (3rd run)	125	24	66	49:51
7	**a**	**1** (4th run)	123	24	70	51:49
8	**a**	**1** (5th run)	~120	24	75	53:47
9	**a**	**1**[c]	60	36	64	42:58
10	**a**	**1**[d]	60	36	90	50:50
11	**a**	**2**	200	12	50	65:35
12	**a**	**2**	340	24	86	65:35
13	**a**	**2** (2nd run)		24	70	63:37
14	**a**	**3** (1st run)	100	24	97	55:45
15	**a**	**3** (2nd run)		24	70	53:47
16	**a**	**3** (3rd run)[e]		24	13	70:30
17	**a**	**3** MeI[f]	85	24	35	57:43
18	**a**	**3** MeI[g]	100	24	43	60:40
19	**a**	**3** Ac_2O[h]	100	24	37	72:28
20	**a**	**4** (1st run)	100	24	75	55:45
21	**a**	**4** (2nd run)		24	40	54:46
22	**a**	**4** (3rd run)	in water	24	traces	n.d.
23	**a**	**5**[i]	10 mol%	24	80	60:40
24	**a**	**6**[j]	10 mol%	24	traces	n.d.
25	**a**	**7**[j]	10 mol%	24	traces	n.d
26	**a**	**8**[i]	10 mol%	24	25%	49:51
27	**a**	**9**[j]	10 mol%	24	75	53:47
28	**b**	**3**	100	24	48	56:44
29	**c**	**3**	100	24	traces	n.d.
30	**d**	**3**	100	24	Traces	n.d.
31	**a**	**3**[k]	100	24	67	60:40

[a] Reaction conditions: aldehyde (0.25 mmol), cyclohexanone (0.5 mL), H_2O (140 μL), 50 °C. [b] Reaction without addition of water at RT. [c] **11** (0.15 mmol), cyclohexanone (0.3 mL), and water (2 mL) were used instead. [d] **11** (0.15 mmol), cyclohexanone (0.3 mL), and phosphate buffer (2 mL of 0.18 M, pH 7) were used instead. [e] Catalysts was washed with HCl (5 mL of 1 M) for 5 min. [f] MeI in EtOH, RT, was used to methylate nucleophilic sites of **3** prior to application. [g] K_2CO_3 and MeI at 50 °C were used to methylate nucleophilic sites of **3** prior to application. [h] Acetic anhydride, triethylamine, MeCN, RT, 24 h was applied to acetylate nucleophilic sites of **3** prior to application. [i] Reactions were performed with 10 mol% of catalyst, aldehyde (1 mM), cyclohexanone (2 mL), H_2O (560 μL), 50 °C and 10 mol% Et_3N. [j] Reaction performed with 10 mol% of catalyst, aldehyde (1 mM), cyclohexanone (2 mL), H_2O (560 μL), 50 °C. [k] MNPs were reacted with 4-nitrobenzaldehyde for 4 days before reaction.

75% yield, just one phenolic hydroxyl group is sufficient for an effective dual catalysis as long as an amino group is present. Based on these observations, the transition state of the C–C bond-forming step of the aldol reaction disclosed in Scheme 2 seems to be a reasonable rationalization for the catalytic effect of PDA. Taking into consideration our observations (v.s.), alternative structural proposals for PDA lacking nucleophilic aminoalkyl groups are less likely to catalyze the aldol reaction.[39]

To obtain more evidence for the involvement of both types of functional groups of PDA in the catalysis, we tried to block them by irreversible reactions with strong electrophiles, such as by methylation with methyl iodide (Table 1, entries 17, 18) or acetylation with acetic anhydride (entry 19) and to check the products in their catalytic behavior. Reaction of PDA with methyl iodide was assumed to methylate the amino groups to quaternary ammonium salts and the hydroxyl groups to methyl ethers.[26] Acetic anhydride could cause analogous blocking of these groups by amide or ester formation, respectively. In our case, the materials obtained after reaction with methyl iodide (entries 17, 18) or acetic anhydride (entry 19) suffered drastic reduction of the catalytic performance. Thus, strong electrophiles affect the catalytic sites in PDA although they do not completely block the catalytic activity. This observation may also be the key for understanding the deactivation of PDA within the first run of the aldol reaction. In these reaction mixtures are found aldehydes and ketones as electrophiles capable of reacting with the amino groups of the PDA. In fact, the reaction of PDA amino groups with the ketone is even necessary to enter the catalytic cycle. It could be that intermediates formed in the catalytic cycle (see Scheme 2) are not cleaved and thus parts of the catalytic amino sites remain blocked or that 4-nitrobenzaldehyde forms a relatively stable imine with PDA thus blocking both the catalytic amino groups of PDA and the aldehyde as reactant.

For a better understanding of the deactivation process, catalysts **3** and **4** were investigated by elemental analysis, FTIR, and XPS after being employed in three cycles of the aldol reaction. Elemental analysis revealed a reduction of the nitrogen content in **3** from 2.96 to 0.61% and in **4** from 0.83 to 0.42%. This is an indication that PDA gets lost from the magnetic nanoparticles. FTIR spectra of used PDA-coated MNPs **3** and **4** showed two new bands (1346 and 1520 cm^{-1}; see Figures 5 and 6). They were assigned to the N–O stretching vibration of nitro groups. This indicated that uptake of 4-nitrobenzalde-



Scheme 2. Rationalization of the mechanistic pathway and the transition state of PDA-catalyzed aldol reactions.

hyde by PDA occurred, presumably by imine formation with the free amino groups of PDA.

The same appearance of new bands (1343 and1520 cm^{-1}) typical for nitro groups was observed when PDA-coated NP **3** were treated only with 4-nitrobenzaldehyde at 50 °C for four days (see Figure 7).

In fact, the appearance of imine and nitro groups was also evidenced in the high resolution N 1s XPS-spectrum showing energy values of 398.5 and 404.8 eV, respectively (see Figure 8 and the Supporting Information for further XPS spectra). Catalytic tests performed with these MNP **3** primarily reacted with 4-nitrobenzladehyded revealing that the yield of aldol product dropped from 97 (Table 1, entry 14) to 67% (entry 31), that is, the material still keeps some of its catalytic properties (compare entry 31 with 14).

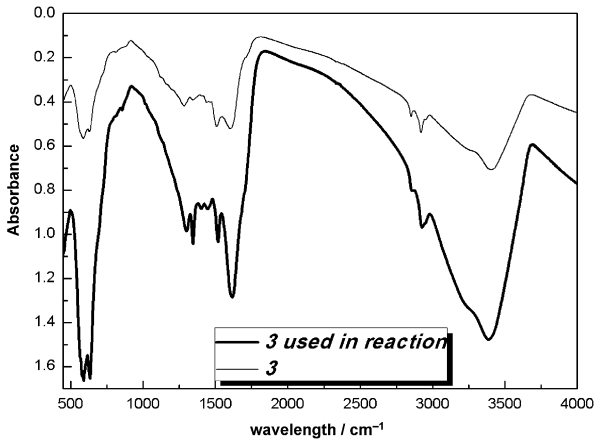


Figure 5. FTIR spectra of **3** before and after use in the aldol reaction.

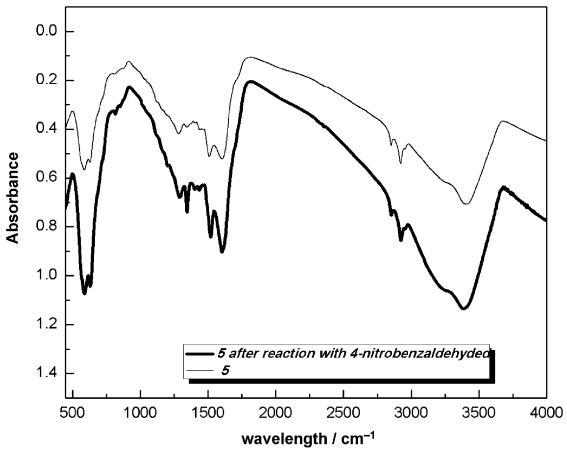


Figure 7. FTIR spectra of **5** before and after reaction with 4-nitrobenzaldehyde for 4 days.

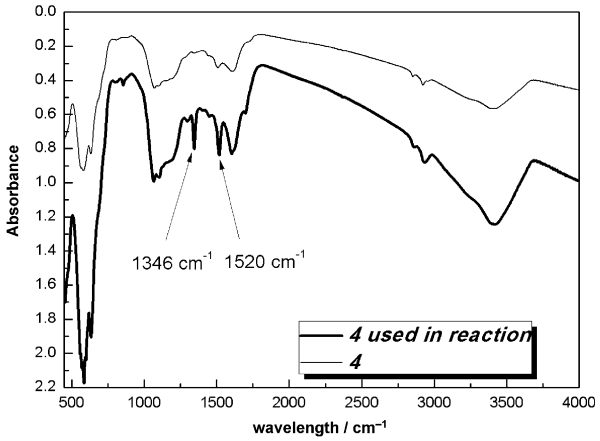


Figure 6. FTIR spectra of **4** before and after use in the aldol reaction.

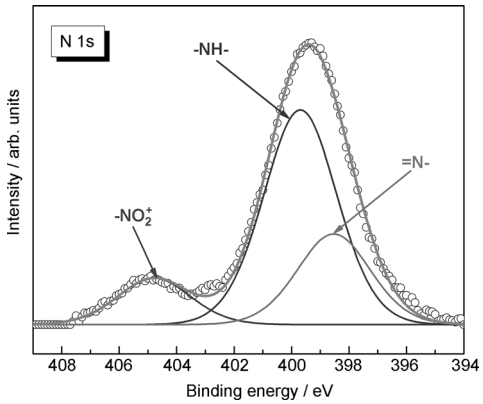


Figure 8. High resolution N 1s XPS spectrum of MNP **3** reacted with 4-nitrobenzaldehyde for 4 days.

These results allow the conclusion that two independent processes are responsible for the deactivation of PDA in aldol reactions: leaching of PDA and blocking of amino groups of PDA by arylaldehyde **11**. The fact that the catalytic performance dropped remarkably only in the first step and remained more or less constant in subsequent steps can be explained by the feature that PDA is not a uniform polymer but contains a mixture of different structures held together not only by covalent bonds but also by hydrogen bonding, wherein eventually amino groups are involved.[19,40] These mixtures can consist of oligomers with relatively many amino groups (premature, less oxidized, noncyclized dopamine units) and of others with less amino groups but more indole structures (matured, more oxidized, cyclized dopamine units, see also Scheme 1). Obviously, the former will show higher catalytic activity than the latter. When the amino groups are involved in the catalytic cycle of an aldol reaction by forming imines or enamines the hydrogen bonding between the subunits of the PDA is suspended and thus premature oligomers can go into the solution, that is, get lost from the magnetic support. The remaining PDA contains less amino groups and is more stable thus explaining the reduced but persistent catalytic activity in the subsequent runs of an aldol reaction.

Conclusion

PDA, used in many biomedical and separation applications, turns out not to be an innocent material; rather, it shows an unexpected and hitherto unknown behavior as an organocatalyst in aldol reactions, a transformation also taking place in biology. Since it is likely that PDA can also catalyze other reactions scientists should be aware that PDA can also exert unwanted side effects when it is applied in biological and medicinal environment. Our results imply that the PDA acts as a dual catalyst employing both the amino groups and the phenolic hydroxyl groups in a combined fashion. PDA was supported on magnetite nanoparticles rendering them as organocatalysts, which were easily recycled by magnetic separation. Investigations using PDA and PDA-coated MNPs as catalysts in other reactions are presently underway in our laboratories.

Experimental Section

General

All reagents were commercially available and used without further purification, unless otherwise stated. Magnetic nanoparticles covered with a chemisorbed oleic acid monolayer with an average size of approximately 7 nm were obtained from the group of Dr. Ladislau Vekas, Romanian Academy - Timisoara branch. Their preparation was reported elsewhere.[41] Magnetic nanoparticles "MagSilica" **10** covered with silica shell were produced by Evonik. Compounds **9–11** were obtained according to reported protocols.[42] ^{1}H and ^{13}C NMR were recorded on a 500 MHz Bruker Avance III spectrometer; chemical shifts (δ) are reported in ppm relative to TMS. Reactions were monitored by TLC. Flash-chromatography was carried out using Merck silica gel 60. The morphology of functionalized MNP was determined by 1010 JEOL transmission electron microscope. FTIR spectra were carried out on a JASCO FTIR 610 spectrophotometer. The magnetic measurements were performed at room temperature using a Vibrating Sample Magnetometer Cryogenics.

Synthesis of MNP 3, 4, and 5

MNP (1 g) covered with one layer of oleic acid were combined with EtOH (150 mL) and sonicated. After magnetic separation, this step was repeated two times. The MNPs were washed with H_2O (50 mL), separated by centrifugation, re-dispersed in tris-buffer (pH 8.5, 500 mL) and sonicated for 30 min. To this vigorously stirred suspension dopamine hydrochloride was added (1 g) followed by stirring at RT in the open air for 24 h. The resulting magnetic nanoparticles **2** were precipitated with EtOH and collected by an external magnet. They were washed with H_2O and EtOH. This step was repeated twice. After drying at 50 °C under vacuum overnight the MNPs **2** were obtained as a black powder. For the synthesis of MNPs **3** and **4**, the initial washing step with EtOH was omitted. Silica-coated MNP (1 g) was used for MNP **4** preparation and MNP **2** (1 g) covered with PDA for the preparation of MNP **3**.

Catalytic test in the aldol reaction

Arylaldehyde **11** (0.25 mmol) was added to the appropriate amount of PDA **1** or MNP-supported PDA **2**, **3**, or **4** (see Table 1). Cyclohexanone (0.5 mL) and water (140 μL) were added and the flask was heated to 50 °C. The mixture was stirred for the required time (see Table 1). MeOH (10 mL) was added and the MNPs were collected by an external magnet or in the case of mere PDA by centrifugation. The washing step was repeated 3 times followed by washing with Et_2O (2×10 mL). The catalyst was removed by magnetic separation or centrifugation (in case of PDA) and dried in the open air before the next run. The separated solutions were evaporated and the product **12** was purified by column chromatography. The structures of the aldol products **12** were confirmed by comparison with published NMR spectroscopic data.

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Keywords: aldol reaction · coatings · magnetic nanoparticles · organocatalysis · polydopamine

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Polymers

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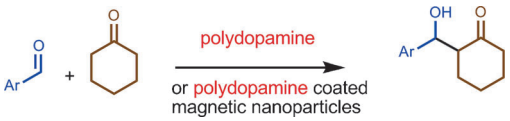
Polydopamine—An Organocatalyst Rather than an Innocent Polymer



Re-evaluating PDA: Polydopamine (PDA) is easily available by oxidation of dopamine and is widely used for persistent coatings of various materials. It is hitherto considered to be inert in many interesting biomedical and other applications. However, results revealed here show that PDA is not an innocent polymer and can act as an organocatalyst in direct aldol reactions under mild conditions (see scheme).