A CO<sub>2</sub>-switchable amidine monomer: synthesis and characterization

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ABSTRACT

Smart system employed CO<sub>2</sub> gas as new trigger has been attracting enormous attention in recent years, but few monomers that are capable of switching their hydrophobicity/hydrophilicity upon CO<sub>2</sub> stimulation have been reported. A novel CO<sub>2</sub>-responsive monomer, 4-vinylbenzyl amidine, is designed and synthesized in this work with N,N-dimethylacetamide dimethyl acetal and 4-vinylbenzyl amine that is prepared through the Gabriel reaction. In bi-phase solvent of n-hexane and water, the monomer dissolves in n-hexane first and then transforms into water upon the CO<sub>2</sub> treatment, indicating a hydrophobic to hydrophilic transition. This transformation is demonstrated as reversible by monitoring the conductivity variation of its wet dimethyl formamide solution during alternate bubbling/removing CO<sub>2</sub>. The protonation of 4-vinylbenzyl amidine upon CO<sub>2</sub> treatment is demonstrated by <sup>1</sup>H NMR which also accounts for the dissolubility change. The reversible addition-fragmentation chain-transfer polymerization of this monomer is also performed, finding the reaction only occurs in glacial acetic acid. The reason can be ascribed to the different radical structure produced in different solvent.

Introduction

CO<sub>2</sub> as a new trigger for smart systems has various advantages over its traditional counterparts such as pH, temperature, redox, light and voltage [1–4]. The first virtue is the good switchability, which means the responsive process can be repeated for much more times without significant attenuation or any contamination into the system [5]. The easy-removing feature of the gas state of CO<sub>2</sub> may account for this characteristic. Furthermore, the CO<sub>2</sub> is a metabolite of living cells rendering it good biocompatibility [6,7]. Last but not the least, CO<sub>2</sub> is a waste gas with wide availability and low price. All these advantages push CO<sub>2</sub>-responsive compounds and polymers into the spotlight [1].

Jessop team [5] first reported a long-chain alkyl amidine compound which worked as a CO<sub>2</sub>-switchable surfactant that can stabilize emulsion under exposing of CO<sub>2</sub> and break the emulsion by bubbling inert gas in higher temperature. Naturally, researchers want to figure out what would happen if the amidines groups are introduced into polymers. Some efforts have been made to achieve CO<sub>2</sub>-responsive polymers by post modification. Take our previous work as an example, we prepared poly(4-chloromethylstyrene) (PCMS) first by reversible addition-fragmentation chain transfer (RAFT) polymerization. Then the chloro groups were transferred into azido units in the second step. Finally, a homemade N′-propargyl-N,N-dimethylacetamidines (PDAA) were coupled with the azido units through a ‘click’ chemical process, yielding amidine-containing polymers [8,9]. Lowe and coworkers [10] synthesized polymers containing pentafluorophenyl acrylate (PFPA) and then substituted the pentafluorophenyl groups with amidine species histamine (HIS), resulting in amidine side chains. Both of these methods can target CO<sub>2</sub>-responsive polymers efficiently, but they seem tedious involving with functionalization after polymerization.

Here in this work, an amidine monomer that is responsive to CO<sub>2</sub> is developed. 4-Vinylbenzyl chloride was first transferred into 4-Vinylbenzylamine through the Gabriel reaction.
In the following step, the colorless transparent crystals (~27.1 g) were dissolved into 50 mL ethanol with heating. Then 12.4 g N\textsubscript{2}H\textsubscript{4}·H\textsubscript{2}O (0.13 mol) was slowly added into the solution, producing white precipitations. After 90 min reaction, white solids were obtained by filtration. Then the solids were dissolved with 15 wt% KOH solution, followed by filtration. The filtrate was extracted for three times with diethyl ether and washed with 2 wt% K\textsubscript{2}CO\textsubscript{3} aqueous solution. Colorless transparent liquid was obtained after drying with K\textsubscript{2}CO\textsubscript{3}, followed by removing solvent with rotary evaporation. \(^1\text{H}\) NMR (\(\delta\), ppm; solvent, CDCl\textsubscript{3}), 3.85 (–CH\textsubscript{2}NH\textsubscript{2}), 5.20–5.24, 5.70–5.74 (–CH=CH\textsubscript{2}), 6.66–6.75 (–CH=CH\textsubscript{2}), 7.2, 7.3 (–C\textsubscript{6}H\textsubscript{4}–CH=CH\textsubscript{2}).

**Synthesis of 4-vinylbenzyl amidine (compound 2)**

6.6 g N,N-Dimethylacetamide dimethyl acetal (45 mmol) was added into 150 mL round-bottom flask, followed by dropping 5.0 g colorless transparent liquid obtained from last step (compound 1) under N\textsubscript{2} protection. The mixture was stirred for 15 min at room temperature and then heated to 65 °C. After 2 h reaction, the product was collected by removing side product methanol and excess N,N-Dimethylacetamide dimethyl acetal with rotary evaporation. \(^1\text{H}\) NMR (\(\delta\), ppm; solvent, CDCl\textsubscript{3}), 1.91 ((CH\textsubscript{3})\textsubscript{2}N– (CH\textsubscript{3})C=N–), 2.95 ((CH\textsubscript{3})\textsubscript{2}N– (CH\textsubscript{3})C=N–), 4.47–4.50 (–C\textsubscript{6}H\textsubscript{4}–CH\textsubscript{2}–N), 5.15–5.29 and 5.59–5.76 (CH\textsubscript{2}=CH–), 6.65–6.74 (CH\textsubscript{2}=CH–), 7.25–7.36 (–C\textsubscript{6}H\textsubscript{4}–).

**Experimental part**

**Materials and characterization**

4-Vinylbenzyl chloride (90%), phthalimide potassium salt (99%), hydrazine monohydrate (N\textsubscript{2}H\textsubscript{4}·H\textsubscript{2}O, 50%), KOH, K\textsubscript{2}CO\textsubscript{3}, N,N-dimethylacetamide dimethyl acetal (90%) 44-azobis(4-cyanovaleric acid) (ACVA; ≥98.0%), were all purchased from Sigma-Aldrich and used without further treatments. The organic solvents of A.R. grade were obtained from Guanghua Sci-Tech Co., Ltd. (Guangdong, China) and used as received. The CO\textsubscript{2} and N\textsubscript{2} gas with a purity of above 99.99% were obtained from the Jinnengda Gas Co. in Chengdu, China. The chain transfer agent (CTA), 4-cyano-4-thiothiopropylsulfanylpentanoic acid (CTPPA), was synthesized according to the previously reported procedures [19,20].

\(^1\text{H}\) NMR spectra were recorded at 25 °C on a Bruker AV300 NMR spectrometer at 300 MHz. The chemical shifts (\(\delta\)) are reported in parts per million (ppm) with reference to the internal standard protons of tetramethylsilane (TMS). The conductivity was determined by an FE30 conductometer (Mettler Toledo, USA) at room temperature.

**Synthesis of 4-Vinylbenzylamine (compound 1)**

In a 250 mL round-bottom flask, 22.9 g 4-vinylbenzyl chloride (0.15 mol) and 27.8 g phthalimide potassium salt (0.15 mol) were dissolved into 100 mL dimethyl formamide (DMF) solution and stored at 50 °C for 4 h with stirring. The solvent was removed by reduced pressure distillation after reaction. Then the mixture was dissolved in CHCl\textsubscript{3} and washed with NaOH solution (0.2 mol·L\textsuperscript{-1}) and water successively. The raw product was concentrated and recrystallized in methanol for two times, yielding colorless transparent crystals.

In the following step, the colorless transparent crystals (~27.1 g) were dissolved into 50 mL ethanol with heating. Then 12.4 g N\textsubscript{2}H\textsubscript{4}·H\textsubscript{2}O (0.13 mol) was slowly added into the solution, producing white precipitations. After 90 min reaction, white solids were obtained by filtration. Then the solids were dissolved with 15 wt% KOH solution, followed by filtration. The filtrate was extracted for three times with diethyl ether and washed with 2 wt% K\textsubscript{2}CO\textsubscript{3} aqueous solution. Colorless transparent liquid was obtained after drying with K\textsubscript{2}CO\textsubscript{3}, followed by removing solvent with rotary evaporation. \(^1\text{H}\) NMR (\(\delta\), ppm; solvent, CDCl\textsubscript{3}), 3.85 (–CH\textsubscript{2}NH\textsubscript{2}), 5.20–5.24, 5.70–5.74 (–CH=CH\textsubscript{2}), 6.66–6.75 (–CH=CH\textsubscript{2}), 7.2, 7.3 (–C\textsubscript{6}H\textsubscript{4}–CH=CH\textsubscript{2}).

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**RAFT polymerization of 4-vinylbenzyl amidine**

The RAFT polymerization is carried out as following typical procedure. 1.02 g 4-vinylbenzyl amidine (5.0 mmol), 14 mg CTPPA (0.05 mmol) and 3 mg initiator ACVA and 2 mL of solvent was added into a reaction tube. Then the system was deoxygenated with three freeze-thaw cycles or bubbling N\textsubscript{2} for 30 min followed by keeping at 70 °C for 24 h. After the reaction, the product was checked with \(^1\text{H}\) NMR.

**Results and discussion**

**CO\textsubscript{2} -responsiveness of 4-vinylbenzyl amidine**

As above-mentioned, we previously developed CO\textsubscript{2}-responsive polymers by combing RAFT polymerization and ‘click’ chemistry, which is not suitable for preparation of complex copolymers, such as multi-block and star structures [8,9]. Therefore, we try to synthesize a CO\textsubscript{2}-responsive monomer in this work. After we confirm the chemical structure of this monomer by NMR (see experimental part), its solubility is tested, finding it can be dissolved in common organic solvent including n-hexane, CH\textsubscript{2}Cl\textsubscript{2}, CHCl\textsubscript{3}, THF, DMF, DMSO. To check out the CO\textsubscript{2}-sensitivity, we then
investigate whether it can transform from organic solvent into water phase, meaning whether it can transition from hydrophobicity to hydrophilicity. As shown in Figure 1, in a bi-phase solvent of n-hexane and water (v/v = 1:1), several drops monomer is added into the system. The monomer is dissolved into n-hexane in upper phase without CO$_2$ treatment, appearing as a yellow solution above water. Then CO$_2$ gas is bubbled into the solution, resulting in a yellow aqueous solution in the bottom. Meanwhile, the upper n-hexane becomes colorless and transparent. The n-hexane is a non-polar solvent, this transition implies the monomer can transform from hydrophobicity into hydrophilicity upon CO$_2$ stimulation.

To confirm the switchability of this monomer, we monitor the conductivity variation of its wet DMF solution during CO$_2$ is bubbling and removing alternately. As shown in Figure 2, the conductivity of the monomer solution jumps from 43.0 to 900.1 μS cm$^{-1}$ after bubbling CO$_2$ for 4 min. Subsequently, it drops back to around 45.6 μS cm$^{-1}$ after removing CO$_2$ by N$_2$ treatment. Furthermore, this jumping-dropping cycle can be repeated for four times without significant attenuation, indicating the CO$_2$-responsiveness of this monomer is reversible. As a comparison, the conductivity of wet DMF solution without monomer inside only increases from 1.6 to 2.4 μS cm$^{-1}$ under the stimulation of CO$_2$, which further proves the switchable transition of the monomer under stimulation of CO$_2$.

Beside the conductivity, we further investigate the reaction of the monomer with CO$_2$ by $^1$H NMR characterization (Figure 3). The monomers were dissolved into wet DMSO-$d_6$ and characterized by $^1$H NMR before and after the treatment of CO$_2$. By comparing the main proton peak around the amidine group, one can easily indentify the significant chemical shift, i.e. $f$-$[\text{C}_6\text{H}_4\text{CH}_2\text{C}=(\text{CH}_3)\text{N}], g[\text{N}=(\text{CH}_3)\text{C}=\text{N}(\text{CH}_3)\text{H}]$, $h[\text{N}=\text{C}(\text{CH}_3)=\text{N}(\text{CH}_3)\text{H}]$ increases from 4.32, 2.84, 1.85 to 4.46, 3.01, 1.95 ppm, respectively. This result proves the protonation of the monomer after reaction with CO$_2$. The protonation reaction is shown in

![Figure 1. The hydrophobic to hydrophilic transformation of 4-vinylbenzyl amidine upon stimulation of CO$_2$. The solvent is n-hexane and water (v/v = 1:1).](image1)

![Figure 2. Conductivity variation of 4-vinylbenzyl amidine in wet DMF solution (~1 v% water) when CO$_2$ and N$_2$ is alternatively bubbling.](image2)

![Figure 3. $^1$H NMR spectra of 4-vinylbenzyl amidine before and after reaction with CO$_2$ and the reaction equation of amidine and CO$_2$. The solvent is wet DMSO-$d_6$.](image3)
Nevertheless, the product appears as cross-linked gel with yellow color rather than polymer dissolved in solution (Figure 4). This gel cannot be dissolved into any solvents. Further improvements of this polymerization are still progressing in our group. Interestingly, the de-oxygenization method really affects the success of this reaction, if comparing entry 3 and 5 in Table 1. The reason may be ascribed to the highly volatile feature of HAc, which make it firstly filling the reaction tube in vacuum that restrains the discharge of oxygen in solution.

Then we come back to the problem, why the 4-vinylbenzyl amidine cannot be polymerized in neutral state without acetic acid? In the presentence of initiator, two kinds of radicals are possible produced; structure 3 and 4 (Figure 5). The radical 3 is more stable then 4, because it forms a huge conjugated structure combining benzene ring and the donor amidine group. That means the 4-vinylbenzyl amidine transforms into radical 3 in organic reaction system, hindering the polymerization we desired. When the amidine groups are protonated by acetic acid, the possible huge conjugated structure 3 cannot form anymore and oxygen (entry 5, Table 1). Nevertheless, the product appears as cross-linked gel with yellow color rather than polymer dissolved in solution (Figure 4). This gel cannot be dissolved into any solvents. Further improvements of this polymerization are still progressing in our group. Interestingly, the de-oxygenization method really affects the success of this reaction, if comparing entry 3 and 5 in Table 1. The reason may be ascribed to the highly volatile feature of HAc, which make it firstly filling the reaction tube in vacuum that restrains the discharge of oxygen in solution.
Table 1. Reaction conditions of RAFT polymerization of 4-vinylbenzyl amidine.

| No. | De-oxygenization | Solvent          | Initiator/CTA | Product       |
|-----|------------------|------------------|---------------|--------------|
| 1   | Freezing-thaw    | HAc/DMF=1:1<sup>a</sup> | 0.2:1         | None         |
| 2   | Freezing-thaw    | HAc              | 0.2:1         | None         |
| 3   | Freezing-thaw    | HAc              | 1:1           | None         |
| 4   | Bubbling N<sub>2</sub> 30 min | HAc | 0.2:1 | None |
| 5   | Bubbling N<sub>2</sub> 30 min | HAc | 1:1 | Cross-linked gel |

<sup>a</sup>Volume ratio. <sup>b</sup>Glacial acetic acid. <sup>c</sup>Molar ratio.

the polymerization occurs through the same mechanism of the radical polymerization of polystyrene. It should be point out that the reported amidine monomers (compounds 5 and 6 in Figure 5) can be polymerized through a radical mechanism in their natural state because they have no concerning to form stable structure like radical 3.

Conclusions

In conclusion, a CO<sub>2</sub>-responsive monomer, 4-vinylbenzyl amidine, was designed and synthesized in this work. It transforms from hydrophobic to hydrophilic state under the stimulation of CO<sub>2</sub>, and this transition is reversible. This monomer can be polymerized by RAFT technique in glacial acetic acid, yielding a gel-like homo-polymer. The results of this work provide another choice for preparing new CO<sub>2</sub> responsive polymers and pave a way to the development of novel CO<sub>2</sub>-sensitive ‘smart’ system.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Darabi A, Jessop PG, Cunningham MF. CO<sub>2</sub>-responsive polymeric materials: synthesis, self-assembly, and functional applications. Chem Soc Rev. 2016;45:4391–4436.
[2] Yan Q, Zhao Y. Block copolymer self-assembly controlled by the “green” gas stimulus of carbon dioxide. Chem Commun. 2014;50:11631–11641.
[3] Lin S, Theato P. CO<sub>2</sub>-responsive polymers. Macromol Rapid Commun. 2013;34:1118–1133.
[4] Liu H, Lin S, Feng Y, et al. CO<sub>2</sub>-responsive polymer materials. Polym Chem. 2017. doi:10.1039/C6PY01101B.
[5] Liu Y, Jessop PG, Cunningham M, et al. Switchable surfactants. Science. 2006;313:958–960.
[6] Yan Q, Zhao Y. CO<sub>2</sub>-stimulated diversiform deformations of polymer assemblies. J Am Chem Soc. 2013;135:16300–16303.
[7] Che N, Yang S, Kang H, et al. Synthesis and properties of CO<sub>2</sub>-switchable Dex-g-PAHMA copolymers. Polym Chem. 2014;5:7109–7120.
[8] Guo ZR, Feng YJ, Wang Y, et al. A novel smart polymer responsive to CO<sub>2</sub>. Chem Commun. 2011;47:9348–9350.
[9] Guo ZR, Feng YJ, He S, et al. CO<sub>2</sub>-responsive “smart” single-walled carbon nanotubes. Adv Mater. 2013;25:584–590.
[10] Quek JY, Roth PJ, Evans RA, et al. Reversible addition-fragmentation chain transfer synthesis of amidine-based, CO<sub>2</sub>-responsive homo and AB diblock (Co) polymers comprised of histamine and their gas-triggered self-assembly in water. J Polym Sci Part A Polym Chem. 2013;51:394–404.
[11] Yan Q, Zhou R, Fu C, et al. CO<sub>2</sub>-responsive polymeric vesicles that breathe. Angew Chem Int Ed. 2011;50:4923–4927.
[12] Yan Q, Wang J, Yin Y, et al. Breathing polymersomes: CO<sub>2</sub>-tuning membrane permeability for size-selective release, separation, and reaction. Angew Chem Int Ed. 2013;52:5070–5073.
[13] Zhang Q, Yu G, Wang W-J, et al. Preparation of N<sub>2</sub>/CO<sub>2</sub> triggered reversibly coagulatable and redispersible latexes by emulsion polymerization of styrene with a reactive switchable surfactant. Langmuir. 2012;28:5940–5946.
[14] Ma Y, Yung L-YL. Detection of dissolved CO<sub>2</sub> based on the aggregation of gold nanoparticles. Anal. Chem. 2014;86:2429–2435.
[15] Han D, Boissiere O, et al. General strategy for making CO<sub>2</sub>-switchable polymers. ACS Macro Lett. 2011;1:57–61.
[16] Zhang JM, Han DH, Zhang HJ, et al. In situ recyclable gold nanoparticles using CO<sub>2</sub>-switchable polymers for catalytic reduction of 4-nitrophenol. Chem Commun. 2012;48:11510–11512.
[17] Kumar S, Tong X, Dory YL, et al. A CO<sub>2</sub>-switchable polymer brush for reversible capture and release of proteins. Chem Commun. 2013;49:90–92.
[18] Han D, Boissiere O, Kumar S, et al. Two-way CO<sub>2</sub>-switchable triblock copolymer hydrogels. Macromolecules. 2012;45:7440–7445.
[19] Convertine AJ, Benoit DSW, Duvall CL, et al. Development of a novel endosomolytic diblock copolymer for siRNA delivery. J. Control Release. 2009;133:221–229.
[20] Xu XW, Smith AE, Kirkland SE, et al. Aqueous RAFT synthesis of pH-responsive triblock copolymer mPEO-PAMPA-PDPAEMA and formation of shell cross-linked Micelles. Macromolecules. 2008;41:8429–8435.
[21] Jessop PG, Heldebrant DJ, Li X, et al. Green chemistry: reversible nonpolar-to-polar solvent. Nature. 2005;436:1102–1102.
[22] Allen MH Jr, Hemp ST, Smith AE, et al. Controlled radical polymerization of 4-vinylimidazole. Macromolecules. 2012;45:3669–3676.