Biocompatible Choline Iodide Catalysts for Green Living Radical Polymerization of Functional Polymers

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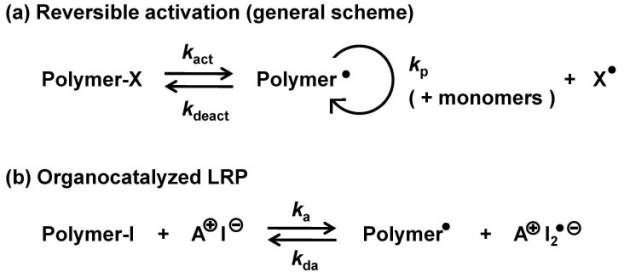
ABSTRACT: Herein, non-toxic and metabolizable choline iodide analogues, including choline iodide, acetylcholine iodide, and butyrylcholine iodide, were successfully utilized as novel catalysts for "green" living radical polymerization (LRP). Through the combination of several green solvents (ethyl lactate, ethanol, and water), this green LRP process yielded low-polydispersity hydrophobic, hydrophilic, zwitterionic, and water-soluble biocompatible polymethacrylates and polyacrylates with high monomer conversions. Well-defined hydrophobic-hydrophilic and hydrophilic-hydrophilic block copolymers were also synthesized. The accessibility to a range of polymer designs is an attractive feature of this polymerization. The use of non-toxic choline iodide catalysts as well as green polymerization conditions provide can contribute to sustainable polymer chemistry.

The synthesis of functional polymers through environmental benign "green" processes has attracted increasing interest.[1,2] The use of chemicals and solvents with minimized toxicities is highly preferable for synthesizing polymers particularly for biomedical applications.[3]

Living radical polymerization (LRP) is a powerful technique for tailoring polymer architectures with predictable molecular weights (or molar masses) and narrow molecular weight distributions.[4–19] LRP is based on the reversible activation of a dormant species (Polymer–X) to a propagating radical (Polymer$^{\bullet}$) (Scheme 1a). Our research group developed organocatalyzed LRP that exploits an alkyl iodide (R–I) as an initiator and an organic molecule as a catalyst.[20–24] Among several effective catalysts, iodide anion (I^-) is one of the most active catalysts and is amenable to a variety of monomers.[21–23] Mechanistically, Polymer–I is activated by I^- to reversibly generate polymer$^{\bullet}$ (Scheme 2b). I^- is used in the form of salts such as tetrabutylammonium iodide ($Bu_4N^+I^-$).[21] This organocatalyzed LRP is attractive because no special capping agents or no expensive catalysts are required.

Scheme 1. Reversible Activation: (a) General Scheme and (b) Organocatalyzed LRP.



The combination of LRP with green chemistry has mushroomed over recent years, particularly for atom transfer radical polymerization (ATRP).[25–29] ATRP uses alkyl halides as initiators and transition-metal complexes (such as copper (I) complexes) as catalysts.[4] The use of heavy metals concerns potential toxicity and extra purification steps. In this regard, the use of less toxic water-soluble copper complexes[30,31], ppm-level copper-catalysts,[32,33] and iron-based catalysts[34–40] were reported as greener approaches, for example. These approaches are able to reduce or eliminate the extra purification steps and contribute to the sustainability aspects in green polymer chemistry.

Choline is an essential vitamin-like nutrient for humans.[41–43] The Food and Nutrition Board of the U.S. Institute of Medicine recommends a daily adequate intake of approximately 500 mg for a human adult.[44,45] An important function of choline is to serve as a precursor of acetylcholine, which is a major neurotransmitter involving in nerve systems and muscle control. Butyrylcholine is a synthetic choline derivative, which is non-toxic and extensively used for clinical researches.[46] Acetylcholine and butyrylcholine are biochemically hydrolysable into choline and short-chain fatty acids in the presence of cholinesterases that are generated in human liver.

The biocompatibility and metabolizability of choline and its analogues inspire us to use them as green catalysts in the organocatalyzed LRP. In the present work, we used choline iodide (ChI), acetylcholine iodide (AChI), and butyrylcholine iodide (BChI) (Figure 1) as non-toxic catalysts for the syntheses of several polymethacrylates and polyacrylates. This approach is an alternative approach to the mentioned ppm-level copper-catalyst and iron-based catalyst systems in the sustainability aspects in green pol-

ymer chemistry. Choline chloride is non-toxic (LD50 ≥ 3150 mg/kg) according to animal studies.[47] A proper amount of iodide such as NaI is also non-toxic and even essential to produce the thyroid hormones thyroxine and triiodothyronine.[48-50] Thus, although there are no quantitative toxicity data of choline iodides, choline iodides consisting of metabolizable choline and iodide would be non-toxic. These choline iodides contain an I^- anion (Figure 1), which plays a catalytic role. Notably, these catalysts are amenable to water-soluble monomers such as zwitterionic monomers, which had been a challenge in the organocatalyzed LRP. The syntheses of hydrophobic-hydrophilic and hydrophilic-hydrophilic block copolymers were also studied.

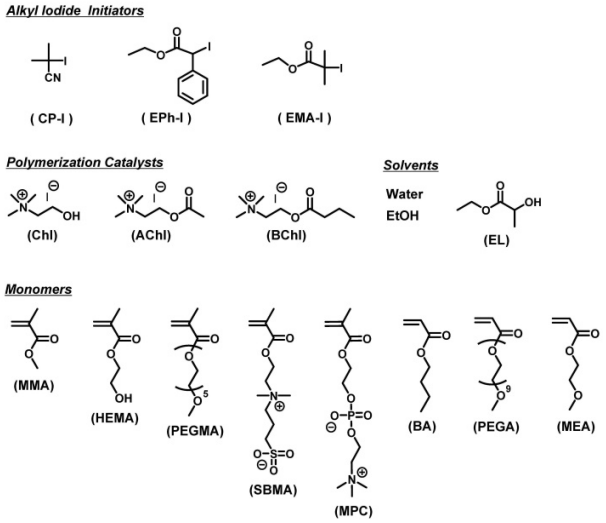


Figure 1. Structures of alkyl iodides, catalysts, solvents and monomers used in this work.

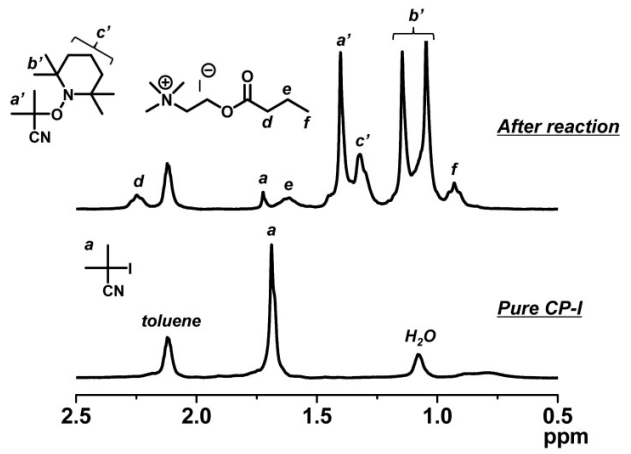


Figure 2. ^{1}H NMR (300 MHz) spectra of pure CP–I and the solution of CP–I (20 mM), BChI (20 mM), and TEMPO (40 mM) heated at 60 °C for 12 h. The solvent was a mixture of toluene-d_8 and acetonitrile-d_3 (9/1).

Prior to the studies on the polymerization, we performed a radical trap experiment[21,51] in a low-mass model system to confirm the generation of the alkyl radical ($R^•$) from an alkyl iodide (R–I) catalyzed by BChI. 2-Iodo-2-methylpropionitrile (CP–I) (Figure 1) was used as an R–I. CP–I (20 mM), BChI (20 mM), and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (40 mM) as a radical trap were heated in a mixed solvent of toluene-d_8 and acetonitrile-d_3 (9/1) at 60 °C. This mixed solvent (dielectric constant = 5.9) is a model of methyl methacrylate (MMA) medium (dielectric constant = 7.9). BChI was completely dissolved in this mixed solvent.

If CP–I reacts with BChI, the generated radical $CP^•$ is trapped by TEMPO, thereby yielding CP–TEMPO. Fig. 2 shows the ^{1}H NMR spectra before and after the reaction. After 12 h, new signals appeared and matched those of pure CP–TEMPO that was independently prepared. The extent of reaction of CP–I to CP–TEMPO was 93%. The result clearly demonstrates the generation of $CP^•$ from CP–I with BChI.

In all polymerizations described below, instead of CP–I, we used α-iodophenylacetate (EPh–I) and ethyl 2-iodo-2-methyl-propionate (EMA–I) as alkyl iodide initiators (Figure 1) so that the synthesized polymers did not bear the toxic nitrile moiety. The polymerization was conducted in bulk or in a green solvent (ethyl lactate (EL), ethanol, or water) in all cases. EL is a non-toxic and biodegradable green solvent used in food, pharmaceutical, and cosmetic industries.[52,53] The catalysts are biocompatible. Therefore, all polymerizations described below are green systems.

Figure 3 and Table 1 (entries 1 and 2) show the polymerizations of MMA and butyl acrylate (BA) (as two representative monomers) using BChI as a catalyst. The bulk polymerization of MMA (8 M) with EPh–I (80 mM) and BChI (80 mM) gave a 73% monomer conversion at 70 °Cfor 10 h. The number-average molecular weight (M_n) agreed with the theoretical value ($M_{n,theo}$), and the polydispersity index ($Đ$) (= M_w/M_n) was approximately 1.2 from an early stage of polymerization, where M_w is the weight-average molecular weight. This result shows the effectiveness of the BChI catalyst. The solution polymerization of BA (8 M) with EMA–I (80 mM) and BChI (320 mM) in 25wt% EL (solvent) gave a 48% monomer conversion at 110 °C for 48 h. Low-polydispersity ($Đ$ = 1.3–1.4) polymers were successfully obtained. Because the carbon–iodine bond in an acrylate polymer (with a secondary alkyl chain end) is stronger than that in a methacrylate polymer (with a tertiary alkyl chain end), highly active catalysts are necessary for acrylate polymerizations. The observed successful use of BChI for the BA polymerization demonstrates the high activity of BChI. EL (solvent) was used for dissolving BChI, because BChI is poorly soluble in bulk BA.

Table 1. Homo- and Block-polymerizations of MMA, BA and Functional Monomers.

Entry	M[a]	R–I	Cat.	Solvent[b]	$[M]_o/[R–I]_o/[Cat.]_o/[V65]_o$ (mM)[c]	T (°C)	t (h)	Conv (%)	M_n[d] ($M_{n,theo}$[e])	$Đ$[d]
1	MMA	EPh–I	BChI	—	8000/80/80/0 (100/1/1/0)	70	10	73	6700 (7300)	1.20
2	BA	EMA–I	BChI	EL	8000/80/320/0 (100/1/4/0)	110	48	48	6000 (6100)	1.30
3	HEMA	EPh–I	ChI	—	8000/80/80/120 (100/1/1/1.5)	50	6	77	17000 (10000)	1.34
4	HEMA	EPh–I	AChI	—	8000/80/80/120 (100/1/1/1.5)	50	4	86	20000 (11000)	1.46
5	HEMA	EPh–I	BChI	—	8000/80/80/120 (100/1/1/1.5)	50	6	76	19000 (9900)	1.45
6	HEMA	EPh–I	ChI	EtOH	8000/80/40/120 (100/1/0.5/1.5)	50	8	67	16000 (8700)	1.28
7	HEMA	EPh–I	AChI	EtOH	8000/80/40/120 (100/1/0.5/1.5)	50	8	78	15000 (10000)	1.29
8	HEMA	EPh–I	BChI	EtOH	8000/80/40/120 (100/1/0.5/1.5)	50	8	75	16000 (9700)	1.31
9	PEGMA	EPh–I	BChI	—	8000/80/40/120 (100/1/0.5/1.5)	50	8	62	19000 (19000)	1.40
10	PEGMA	EPh–I	ChI	Water	8000/80/160/80 (100/1/2/1)	50	1.5	70	28000 (21000)	1.40
11	PEGMA	EPh–I	AChI	Water	8000/80/80/80 (100/1/1/1)	50	2	71	27000 (23000)	1.42
12	PEGMA	EPh–I	BChI	Water	8000/80/80/80 (100/1/1/1)	50	2.5	65	26000 (20000)	1.35
13	MEA	EMA–I	BChI	—	8000/80/80/0 (100/1/1/0)	110	24	52	5500 (6800)	1.31
14	PEGA	EMA–I	BChI	—	8000/160/320/0 (50/1/2/0)	110	24	51	11000 (12000)	1.16
15	MPC	EPh–I	AChI	EtOH	8000/80/160/40 (100/1/2/0.5)	55	2	89	21000 (26000)	1.43
16	MPC	EPh–I	BChI	EtOH	8000/80/160/40 (100/1/2/0.5)	55	2	72	23000 (21000)	1.29
17	SBMA	EPh–I	ChI	Water	8000/160/160/160 (50/1/1/1)	55	6	52	7600 (7300)	1.42
18	PEGMA	PMMA–I[f]	AChI	EL	8000/80/80/80 (100/1/1/1)	50	4	89	15000 (31000)	1.19
19	HEMA	PMMA–I[f]	AChI	EL	8000/80/80/80 (100/1/1/1)	50	4	59	11000 (12000)	1.16
20	MMA	PPEGMA–I[f]	BChI	EL	8000/80/80/40 (100/1/1/0.5)	60	4	99	14000 (21000)	1.23
21	MPC	PPEGMA–I[f]	BChI	EtOH	8000/80/160/40 (100/1/2/0.5)	55	2	38	13000 (20000)	1.30

[a]Monomer. The structures of the monomers are given in Figure 1. [b]Diluted with 25wt% EL (entry 2) and 50wt% solvent (entries 6–8, 10–12, and 15–21). [c]Equivalents to R–I are given in the parenthesis. [d]PMMA-calibrated THF-GPC values for entries 1, 2, and 13. PMMA-calibrated DMF-GPC values for entries 3–12, 14, and 18–20. PEG-calibrated water-GPC values for entries 15–17. PMAA-calibrated water-GPC values for entry 21, where PMAA is poly(methacrylic acid). [e]Theoretical M_n calculated with $[Monomer]_o$, $[R–I]_o$, and monomer conversion. [f]M_n = 4400 and $Đ$ = 1.15 for PMMA–I and M_n = 11000 and $Đ$ = 1.21 for PPEGMA–I.

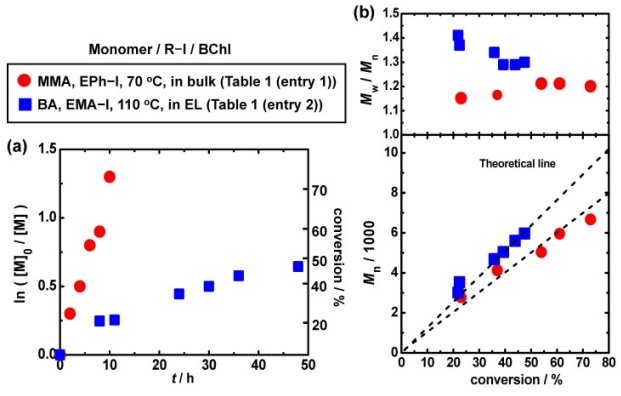


Figure 3. Plots of (a) $\ln([M]_o/[M])$ vs t and (b) M_n and M_w/M_n vs conversion for the MMA/EPh–I/BChI (70 °C) and BA/EMA–I/BChI/EL (110 °C) systems. The reaction conditions are given in Table 1 (entry 1 for the MMA system and entry 2 for the BA system). The symbols are indicated in the figure.

The choline iodide catalysts are salts and well dissolved in polar media such as water and short-chain alcohols. Taking advantage of the high catalytic activity and high solubility in polar media, we utilized the choline iodide catalysts in the polymerizations of 2-hydroxyethyl methacrylate (HEMA), poly(ethylene glycol) methyl ether methacrylate (PEGMA), 2-methoxyethyl acrylate (MEA), poly(ethylene glycol) methyl ether acrylate (PEGA), 2-methacryloyloxyethyl phosphorylcholine (MPC), and [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl) ammonium hydroxide (sulfobetaine methacrylate (SBMA)) (Figure 1). These monomers are used for biomedical applications.[54–56] A relatively low temperature (55 °C or below) was set for the methacrylates to suppress the elimination of HI from the polymer chain end (a side reaction) which can significantly occur in polar media. An azo initiator, 2,2'-azobis(2,4-dimethyl-valeronitrile) (V65), was added to increase the polymerization rate (R_p) at these relatively low temperatures. Azo initiators are frequently used to decrease the deactivator concentration and hence effectively increase the R_p in ATRP and nitroxide-mediated polymerization.[19] In Table 1, the M_n and $Đ$ val-

ues were obtained with PMMA-calibrated GPC for entries 1–14 and PEG-calibrated GPC for entries 15–17, where PMMA is poly(methyl methacrylate) and PEG is poly(ethylene glycol).

The polymerizations of HEMA (Table 1 (entries 3–8)) were conducted in bulk and in ethanol (solvent). Low-polydispersity ($Đ$ = 1.28–1.46) polymers were yielded within 8 h (monomer conversion = 67–86%) using the ChI, AChI, and BChI catalysts. The polymerizations of PEGMA (Table 1 (entries 9–12)) were also successful ($Đ \leq 1.42$) in both bulk and water (solvent). The efficient work of the catalysts in water is intriguing, since the use of water as a solvent had been a challenge in the organocatalyzed LRP. As well as the functional methacrylates, functional acrylates were successfully used (Table 1 (entries 13 and 14)). The polymerizations of MEA and PEGA yielded low-polydispersity ($Đ$ = 1.16–1.31) polymers using BChI.

Zwitterionic polymers contain equal amounts of anionic and cationic groups along their polymer chains and find various applications including ion exchange, sewage treatment, absorption of metal ions, pigment retention, and cosmetic additives.[57,58] Zwitterionic polymers also show unique biological properties, as MPC polymers exhibit hemocompatibility,[59] and SBMA polymers prevents nonspecific adsorption of microorganisms.[60–62] Therefore, zwitterionic polymers are of importance and, in particular, their controlled syntheses in green conditions are highly desirable for biomedical and personal care applications. Table 1 (entries 15–17) shows the polymerizations of MPC and SBMA. The use of the ChI, AChI, and BChI catalysts gave low-polydispersity polymers ($Đ$ = 1.29–1.43) up to reasonably high monomer conversions (52–89%). This is the first controlled synthesis of zwitterionic polymers via the organocatalyzed LRP.

Exploiting the living character and high monomer versatility, hydrophobic-hydrophilic and hydrophilic-hydrophilic block copolymers were synthesized. Staring from the purified PMMA–I macroinitiator (M_n = 4400 and $Đ$ = 1.15), the polymerizations of PEGMA and HEMA yielded well-defined hydrophobic-hydrophilic block copolymers (M_n = 15000 and $Đ$ = 1.19 and M_n = 11000 and $Đ$ = 1.16, respectively) using the AChI catalyst (Table 1 (entries 18 and 19)). A large fraction of the macroinitiator chains extended to block copolymers, indicating high block-efficiency (Figures 4a and 4b). Instead of the PMMA–I macroinitiator, we could also use a hydrophilic PPEGMA–I macroinitiator (M_n = 11000 and $Đ$ = 1.21) to obtain an MMA/PEGMA block copolymer (M_n = 14000 and $Đ$ = 1.23) using the BChI catalyst (Table 1 (entry 20) and Figure 4c), where PPEGMA is poly(poly(ethylene glycol) methyl ether methacrylate). Using the PPEGMA–I macroinitiator, the polymerization of MPC afforded a hydrophilic-hydrophilic block copolymer with low polydispersity (M_n = 13000 and $Đ$ = 1.30) using the BChI catalysts (Table 1 (entry 21) and Figure 4d). These results suggest that this green system is applicable to a variety of block copolymers for biomedical use.

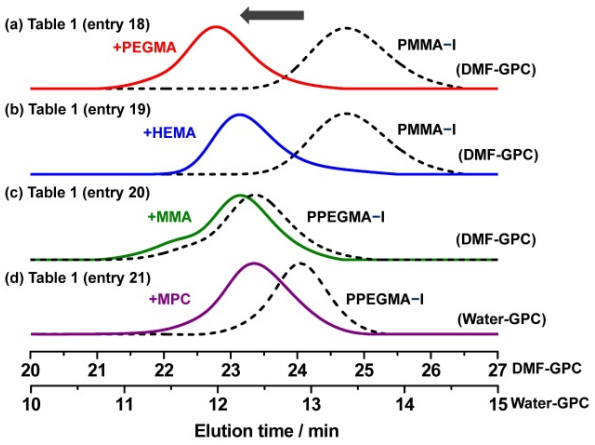


Figure 4. GPC chromatograms before (dashed lines) and after (solid lines) the block copolymerizations in Table 1 (entries 18 to 21).

In summary, non-toxic and metabolizable choline iodides (ChI, AChI, and BChI) were successfully used as catalysts in the organocatalyzed LRP. The amenable monomers encompassed MMA, BA, and hydrophilic biocompatible methacrylates and acrylates. Well-defined block copolymers were synthesized. The accessibility to a wide range of polymer designs is an attractive feature of this polymerization. The choline iodide catalysts are compatible with green solvents (EL, ethanol, and water), offering a green LRP process using chemicals with minimized toxicity to human health and the environment. This green organocatalyzed LRP is completely free from metals and may be practically useful for biomedical applications. The choline iodide catalysts afford a broad monomer scope to water-soluble monomers, which was challenging in our previous NaI-catalyzed polymerization system.[23] The choline iodide catalysts are commercially available, inexpensive, and easy-to-handle and may be attractive for practical use.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org."
Experimental procedures, polymerization data, NMR spectra.

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Notes

The authors declare no competing financial interest.

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