

Multicomponent Combinatorial Polymerization via the Biginelli Reaction

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S Supporting Information

ABSTRACT: A multicomponent combinatorial polymerization method has been exploited as a new intersection between combinatorial chemistry, polymer chemistry, and organic chemistry. The tricomponent Biginelli reaction has been employed as a model multicomponent reaction (MCR) to efficiently prepare a library of polycondensates with continuously changed chain structure but different physical properties. The naturally increased reaction modules (monomers) directly doubled the number of polymers in the library, effectively improving the efficiency of polymer preparation. The glass transition temperatures (T_g) of those homologous polymers have been mapped for the first time to predict the T_g values of absent polymer homologues with good to excellent accuracy. Meanwhile, the T_g maps have also been used to reveal the regular change in T_g according to the polymer structure (linking group, monomer chain length, etc.), initially suggesting the academic significance of the multicomponent combinatorial polymerization system. We believe that the current research paves a straightforward way to synthesize new libraries of polymers via MCRs and might prompt the broader study of MCRs in interdisciplinary fields.

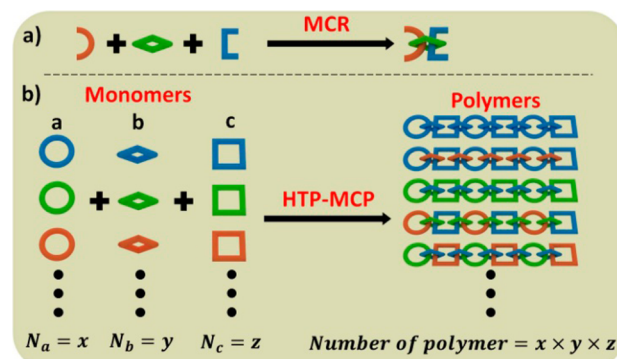
Combinatorial synthesis is a very powerful strategy to rapidly prepare libraries of large numbers of analogous compounds (tens to thousands to even millions) by combination of different reactive modules.^{1–4} As a result, combinatorial synthesis has been applied in many fields, such as peptide synthesis, drug discovery, catalyst research, materials science, etc., to considerably improve the efficiency of synthesis, optimization, and screening of the target products.^{5–12} In polymer chemistry, the concept of combinatorial synthesis has also been introduced to develop some delicate high-throughput (HTP) polymerization systems. By the use of different combinations of analogous monomers, libraries of homologous polymers have been rapidly prepared in a time- and labor-saving manner, thus accelerating the process to achieve proper functional polymers as drug carriers, tissue engineering scaffolds, microdevices, etc.^{13–25} Nowadays, HTP polymerization has been recognized as a potent tool to bridge the gap between the laboratory bench and real life. Thus, developing new HTP polymerization systems to obtain polymers with

more molecular diversity is a challenging subject in methodological investigation and has practical value.

Recently, Meier and co-workers synthesized polycondensates via the tricomponent Passerini reaction,^{26–29} triggering research enthusiasm for multicomponent reactions (MCRs) in polymer chemistry. More and more MCRs, including the Passerini,^{30,31} Ugi,^{32–35} Biginelli,^{36–39} Kabachnik–Fields,^{40–43} Hantzsch,^{44,45} and Mannich^{46,47} reactions, have been reassessed by polymer chemists to prepare new polymers. Polymerization via MCR (MCP) inherits the unique charm of MCRs to offer more molecular diversity to polymers,^{35,43} such as the preparation of six polymers via the Ugi reaction by combinations of four monomers (two bifunctional, two monofunctional).³⁵ At present, MCP is becoming a new, vibrant branch in modern polymer chemistry.

MCRs contain more than two reaction modules (Scheme 1a) and thus are naturally suitable for HTP synthesis systems.

Scheme 1. (a) MCR; (b) HTP-MCP



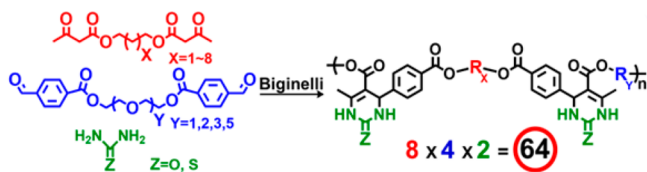
Herein we report for the first time a new combinatorial polymerization system combining HTP polymerization and MCP (HTP-MCP) (Scheme 1b). According to the principle of combinatorial synthesis, the number of polymers is determined by the combination numbers of the monomers in HTP polymerization systems. Therefore, compared with traditional HTP polycondensation systems, which are constructed through two-component coupling reactions, the HTP-MCP system has

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natural superiority to prepare more polymers because of the innately increased number of monomers. As a concrete example, the famous Biginelli reaction was employed in the current research to establish an HTP-Biginelli polycondensation system (Scheme 2).

Scheme 2. HTP-Biginelli Polycondensation System



The tricomponent Biginelli reaction contains three reaction modules (aldehyde, β -keto ester, and (thio)urea or their derivatives) and generates dihydropyrimidin-2H-ones (DHPMs) as products. Previous research verified that the Biginelli reaction is a highly efficient polycondensation tool for the rapid preparation of poly(DHPM)s,^{37–39} which have some attractive properties, such as metal-bonding ability³⁹ or high glass transition temperature (T_g),³⁷ suggesting MCP as a new strategy to realize new applications of MCRs. In the current research, four dialdehyde compounds ($A_2(X)$) and eight bis(β -keto ester) derivatives ($B_2(Y)$) were used as the monomers, and the HTP-Biginelli system was constructed by mixing the $A_2(X)$ and $B_2(Y)$ monomers via different combinations in the presence of urea (C(1)) or thiourea (C(2)) to simultaneously synthesize 32 $A_2(X)B_2(Y)C(1)$ or 32 $A_2(X)B_2(Y)C(2)$ polymers (Figure 1a).

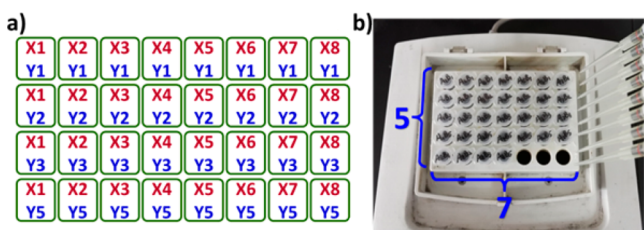


Figure 1. (a) The 32 combinations of $A_2(X)$ and $B_2(Y)$ monomers. (b) Experiment setup for HTP-Biginelli polycondensation (32 samples in 35 positions, with three empty positions).

The polymerization is highly efficient and easy to perform because of the robust Biginelli reaction and thus can be easily carried out in centrifuge tubes in a homothermal shaker (Figure 1b). According to our previous research,^{38,39} the polymerization conditions were chosen as 100 °C using acetic acid and $MgCl_2$ (20% with respect to aldehyde) as the solvent and catalyst, respectively. When urea was used as the third monomer, the molar ratio of monomers was set as $A_2(X):B_2(Y):urea = 1:1:3$; 50% excess urea, which can be easily washed out with water after polymerization, was used to ensure rapid polycondensation.

After addition of the monomers, catalyst, and solvent, 32 tubes were kept in a shaker (100 °C) for 24 h. Samples were taken at different time points for 1H NMR and gel-permeation chromatography (GPC) analyses to monitor the polymerizations. For example, when $A_2(8)$, $B_2(5)$, and urea were used as the monomers (Figure 2a), the monomer conversion was calculated by comparing the integral values for the protons on the benzene ring in $B_2(5)$ monomer and the newly formed

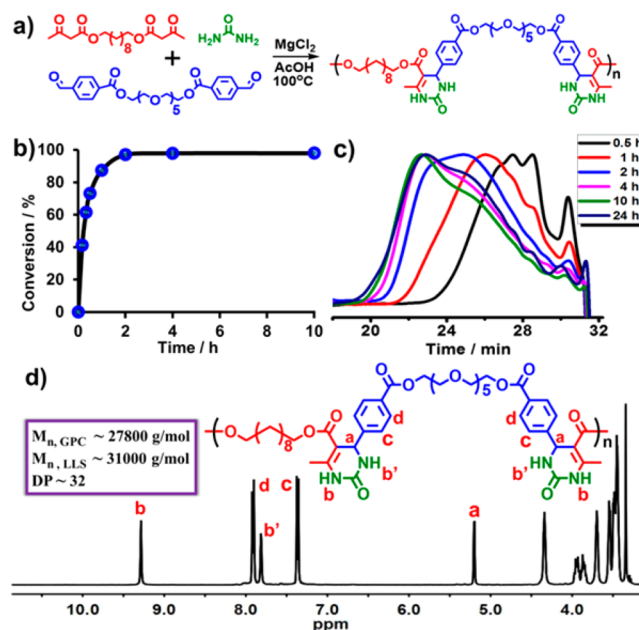


Figure 2. (a) Reaction conditions: acetic acid as solvent, 100 °C, $A_2(8):B_2(5):urea:MgCl_2 = 1:1:3:0.2$. (b) Conversion of the Biginelli reaction vs. time. (c) GPC curves during Biginelli polycondensation. (d) 1H NMR spectrum (DMSO- d_6 , 400 MHz) of the final $A_2(8)B_2(5)C(1)$ polymer.

specific Biginelli methine protons (PhCH, ~ 5.21 ppm) (Figure S1). The monomer was quickly consumed ($\sim 90\%$ in 60 min) (Figures 2b and S1), and only oligomers formed during that period (Figure 2c). Afterward, the monomer conversion quickly reached the maximum ($\sim 100\%$ in 120 min) (Figures 2b and S1), and the polymers had rapidly increased molecular weights at the late stage of the polymerization (Figure 2c), confirming the mechanism of step-growth polymerization. The polycondensation was almost finished in 10 h, and the molecular weight only slightly increased after 24 h (Figure 2c).

Through simple precipitation into cold water to remove the acetic acid and other small molecules (urea, $MgCl_2$, etc.) and washing with diethyl ether, 32 polymers could be easily obtained for further analyses. As a typical example, from the 1H NMR spectrum of the purified $A_2(8)B_2(5)C(1)$ polymer (Figure 2d), the aldehyde group (10.1 ppm) almost completely disappeared, and the characteristic peaks of the Biginelli cyclization product (PhCH, 5.21 ppm; NH, 7.81 and 9.29 ppm) could be clearly identified. The integral ratio of the PhCH methine proton and the protons of the benzene ring ($I_{5.21}:I_{7.37}:I_{7.91} = 1:2:2$) is consistent with the theoretical value (1:2:2), indicating the efficient and thorough Biginelli reaction. The molecular weight of the $A_2(8)B_2(5)C(1)$ polymer was detected using a multiangle laser light scattering (MALLS) detector as $M_{n,LLS} \sim 31\,000$ g/mol ($dn/dc = 0.055$), and thus, the polymerization degree (DP) could be deduced as ~ 32 . All of the polymers had the expected structures (unpresented data) and high molecular weights (Table S1), and MALDI-TOF-MS analysis of an oligomer ($A_2(8)B_2(4)C(1)$) as the model also indicated that the polymer had the designed structure (Figure S2), confirming the successful construction of the HTP system via the Biginelli reaction.

Similarly, when thiourea was used to repeat the polycondensation, the other 32 polymers were readily prepared after 24 h. A polymerization study using $A_2(8)$, $B_2(5)$, and C(2)

as model monomers also confirmed the polycondensation process (Figures S3 and S4), and all of the polymers were formed through Biginelli polycondensation (containing ~17–29% isomer; Figure S3d, using the $A_2(8)B_2(5)C(2)$ polymer as an example) and had satisfactory molecular weights (Table S2). Thus, the total number of polymers was doubled to 64 simply by changing the third monomer, suggesting that introducing MCRs into HTP polymerization is a straightforward way to improve the synthesis efficiency.

The T_g values of the 64 polymers were recorded (Tables S1 and S2) to summarize their change trend with respect to the polymer chain. For example, when $A_2(8)$, $B_2(1,2,3,5)$, and $C(1)$ were used, the correlation between T_g (Figure S5a) and the value of the Y number was found to accord with an exponential decline regularity (Figure 3a, black points). To test the

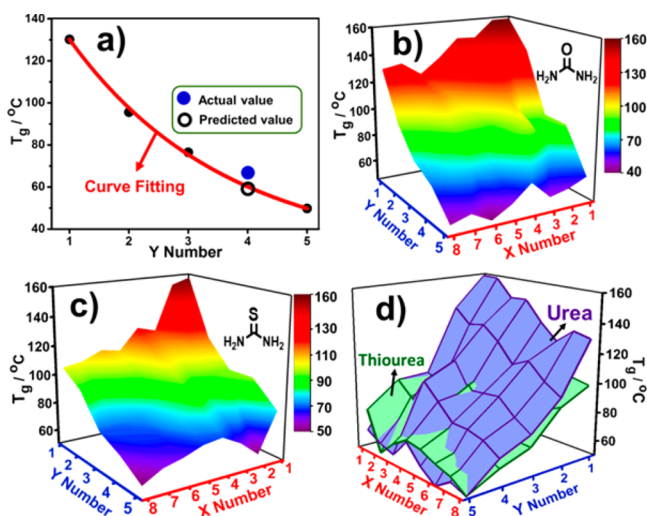


Figure 3. (a) Simulation curve based on the T_g values of $A_2(8)B_2(1,2,3,5)C(1)$ polymers (black points) and the comparison between the predicted (open circle) and actual (blue point) T_g values for $A_2(8)B_2(4)C(1)$. (b) T_g map for the $A_2(X)B_2(Y)C(1)$ polymers. (c) T_g map for the $A_2(X)B_2(Y)C(2)$ polymers. (d) Merged T_g maps (blue, $A_2(X)B_2(Y)C(1)$; green, $A_2(X)B_2(Y)C(2)$).

reasonability of that regularity, monomer $B_2(4)$ was polymerized with $A_2(8)$ and urea, and the T_g of the obtained $A_2(8)B_2(4)C(1)$ polymer was measured as 64.3 °C (Figure 3a, blue point), which is similar to the predicted value (60.2 °C; Figure 3a, open circle). Furthermore, all of the curves of T_g versus Y number with different $A_2(X)$ were drawn, and a list of $A_2(X)B_2(4)C(1)$ polymers were prepared to test the fitting effect (Figure S6). The relative errors (δ) between the expected and experimental values are in the good to excellent range (~4–15%; Table S3), providing a preliminary indication of the rationality of that inductive method. The large deviations ($\delta > 10\%$) might come from the rigid Biginelli ring, which limits the movement of the spacers, especially the short spacers.

Similar results (Figure S5b) were also observed when thiourea was used (Figure S7 and Tables S2 and S4), and most of the predicted T_g values were found to wonderfully coincide with the experimental results ($\delta < 5\%$), further suggesting the reliability of this statistical method.

After the T_g values of those 40 urea-containing polymers (8 × 5 samples) were collected, a 3D map of T_g versus the X and Y numbers (T_g -X-Y for C(1)) was created (Figure 3b). Similarly, another 3D map (T_g -X-Y for C(2)) was also

made for the 40 thiourea-containing polymers (Figure 3c). From both maps, the T_g values were found to reasonably decrease with increasing spacer length of the monomers (softer spacers). After those two maps are merged (Figure 3d), it can clearly be seen that most of the urea-containing polymers have higher T_g values than their thiourea-containing counterparts, which was also observed in our previous research and attributed to the more rigid urea-containing DHPM moiety.⁴⁵ However, some unexpected inversion points can also be observed (Figure 3d). That interesting phenomenon should be a result of multiple factors (type, size, and rigidity of the coupling groups; distance between coupling groups; molecular weights of the polymers; etc.) and suggests the limitation of the analysis based on a small number of samples. Therefore, the HTC-MCP system, which can easily increase the number and diversity of polymer samples, should be valuable for more precise analysis and better understanding of the physical properties of polymers.

In summary, a multicomponent combinatorial polymerization system has been successfully constructed by the combination of HTP polymerization and the tricomponent Biginelli reaction. After two procedures, 64 polymer homologues were readily prepared by changing the reaction modules. T_g maps for those Biginelli polymers have been drawn and used to predict the T_g values of unprepared polymers with satisfactory accuracy. Meanwhile, some unexpected T_g results have also been discovered, suggesting the significance of analyzing a large number of samples and the value of the HTP-MCP system in polymer science. As isourea, isothiurea, and monosubstituted derivatives of urea and thiourea can also be used as modules in the Biginelli reaction,⁴⁸ a polycondensate using $A_2(8)$, $B_2(4)$, and *N*-methylthiourea as the monomers has also been successfully prepared (Figure S8), showing that the current HTP-Biginelli polycondensation system has the potential to be upgraded to further expand the type and number of polymers.

Besides the HTP synthesis, the HTP analysis is also crucial to achieve the benefits of HTP. Thus, the HTP-MCP system still has improvement space by utilizing some advanced analysis technologies, such as the microfluidic method, or including functions suitable for HTP analysis, such as optical properties, stimulus responsiveness, antibacterial ability, etc. Furthermore, the synthesis of polymers via MCRs is growing as a hotspot in polymer chemistry, and many MCRs have been exploited to prepare elegant polycondensates. Thus, this first reported HTP-Biginelli polycondensation system might prompt the development of other HTP-MCP systems based on different MCRs (Ugi, Passerini, Mannich, Hantzsch, etc.) and will lead to the appearance of huge numbers of homologous MCR polymers with interesting characters in the foreseeable future.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04425.

Detailed monomer syntheses, polymerization procedures, and ¹H NMR and T_g results for polycondensates (PDF)

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Notes

The authors declare no competing financial interest.

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