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Polyaldol Synthesis by Direct Organocatalyzed Crossed Polymerization of Bis(ketones) and Bis(aldehydes)

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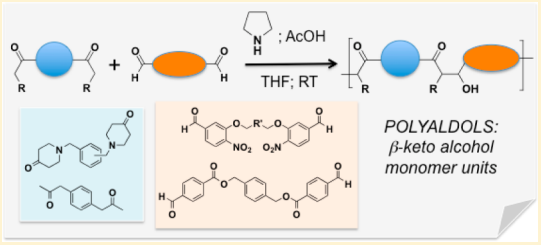
Supporting Information

ABSTRACT: Synthesis of polyaldols consisting of β-keto alcohol monomer units is described. These polymers were obtained by direct step-growth polymerization of purposely designed bifunctional enolizable bis(ketone) monomers playing the role of nucleophilic donors, and activated nonenolizable bis(aldehyde)s serving as electrophilic acceptors. Monofunctional ketone and aldehyde homologues were first synthesized as models to establish the aldol reaction conditions using reaction partners at stoichiometry. A bifunctional organocatalytic system consisting of pyrrolidine in conjunction with acetic acid allowed performing polyaldolizations of stoichiometric amounts of the bis(aldehyde) and the bis(ketone) in solution in THF, DMSO, or DMF, at room temperature. However, polar solvents and/or prolonged reaction time induced further aldol reactions between aldol units of polymer chains, as indicated by the relatively broad molecular weight distribution of related polyaldols observed by size exclusion chromatography. Analysis by NMR spectroscopy confirmed the formation of β-keto alcohol units, but also evidenced that the latter were also partly dehydrated into conjugated ketones via a crotonization reaction (from 20 to 33% depending on the structure of the initial monomers).



INTRODUCTION

The aldol reaction is an extremely popular C−C bond forming addition reaction that is generally catalyzed by a Brønsted or Lewis acid or base, yielding a β-ketohydroxy adduct.[1−4] The term aldolization has been generalized to the addition reaction of any enolizable carbonyl-containing nucleophilic reagent (in general a ketone) onto an electrophilic nonenolizable substrate (mostly aldehydes).[5] Formation of a nucleophilic enolate, prior to its reaction with the aldehyde, is also common and refers to as the indirect aldolization. To this end, silylenol ethers have been extensively employed in the so-called Mukaiyama−aldol reaction.[6−8] The aldol adduct can yet undergo a dehydration (called crotonization) and be converted into the corresponding α,β-unsaturated carbonyl derivative, the driving force being the formation of a conjugated system.[1−4]

An asymmetric carbon atom is also created during aldolization, and control of the stereochemistry of the aldol reaction has been the focus of extensive studies.[9−11] Naturally occurring enzymes, such as aldolases of type I or II, can trigger the aldol formation, via a cooperative stereospecific mechanism.[12] Chiral organometallic catalysts[13] and, more recently, small chiral organocatalysts[4] have been developed for asymmetric aldolization of prochiral substrates. A representative example is the synthesis of the Wieland−Miescher ketone (WMK), a bicyclic diketone (enedione) developed in 1970 at the industrial scale, via an enantioselective aldol process employing L-proline as an organocatalyst.[14−17] This reaction is known as the Hajos−Parrish−Eder−Sauer−Wiechert reaction[18] and is considered as the origin of asymmetric organocatalysis.[4,19−21]

In polymer chemistry, only a few examples of polyaldol synthesis, by repetition of aldol condensation reactions (= polyaldolization), have been reported.[22−28] However, these examples deal with the self-polymerization of aldehydes or ketones. For instance, self-polyaldolization of acetaldehyde catalyzed by Na/Hg amalgam or amines or transition metals led to poly(vinyl alcohol),[22−24] though the polymer also contained vinylidene units due to partial dehydration of vinyl alcohol units. The latter feature was exploited to derive π-conjugated polymers. Thus, a polyol precursor obtained by self-polyaldolization of 5-methylfuran-2-carbaldehyde readily dehydrated into poly(2,5-furandiylvinylene).[25] Kreja et al. further applied this approach to synthesize poly(2,5-thienylenevinylene) and related copolymers.[26] On the other hand, Cataldo reported that a solid resin was obtained by polyaldolic condensation of acetone in the presence of H_2SO_4,

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CF_3SO_3H, or $AlCl_3$.[27] The structure of the polymers resembled that of poly(methylacetylene) incorporating carbonyls and hydroxyls in the main chain. With bases as catalysts (e.g., NaOH or NaOEt) to trigger acetone polymerization, it was shown that isophorone was the first acetone condensation product, the obtained resin eventually resulting from both the condensation of acetone with isophorone and the self-condensation of isophorone.[28]

Alternatively, Itsuno's group developed an indirect synthetic pathway to polyaldols by repeated crossed Mukaiyama−aldol reactions between bis(silylenolether) and bis(aldehyde) monomers.[29−31] Specific chiral Lewis acids allowed synthesizing optically active polyaldols by asymmetric step-growth polymerization. More generally, only a few examples of step-growth polymerization of bis(aldehyde)s have been reported.[32] Itsuno et al. investigated the asymmetric Hosomi-Sakurai polyaddition of bis-allylsilanes and bis(aldehyde)s, forming chiral polymers consisting of allylic alcohol monomer units.[31−37] Aromatic polyesters could be synthesized by direct polyaddition of bis(aldehyde)s,[38−41] involving repeated disproportionation Tishchenko[42,43] reactions between aldehyde functions. More recently, the group of Klok applied the Baylis−Hilman reaction in step-growth polymerization of bis(aldehyde)s and bis(acrylate)s, leading to polyesters featuring allylic units.[44,45] Not only linear polymers but also hyperbranched polyesters were derived.[46] Finally, the direct polyaddition of bis(aldehyde)s catalyzed by a cyanide anion or by *N*-heterocyclic carbenes, as a means to access so-called polybenzoins, was also described.[47−49]

Here we report a novel synthetic strategy to polyaldols, by repetition of direct intermolecular aldolization reactions between properly selected bis(aldehyde) and bis(ketone) monomers. These polyaldolization reactions were triggered via an organocatalyzed pathway utilizing pyrrolidine in conjunction with acetic acid. To the best of our knowledge, although the amine-catalyzed direct intermolecular aldol reaction between a ketone and an aldehyde is extremely well documented in molecular chemistry, the application of this elementary reaction to polyaldol synthesis has never been reported.

EXPERIMENTAL SECTION

Materials. All reagents and solvents were of commercial grade and used as received. Deuterated solvents for NMR spectroscopy were acquired from Armar Chemicals (Dottigen, Switzerland). 1-Benzyl-4-piperidone (**1**, 99%, Sigma-Aldrich), *p*-nitrobenzaldehyde (**2a**, 99.5%, Sigma-Aldrich), 4,4′-pentamethylenebis(acetophenone) (**8**, 99%, Sigma-Aldrich), 4-formylbenzoic acid (≥95.0%, Sigma-Aldrich), benzyl bromide (98%, Sigma-Aldrich), 4-piperidone hydrochloride (98%, Sigma-Aldrich), 1,3-bis(bromomethyl)benzene (97%, Sigma-Aldrich), 1,4-bis(bromomethyl)benzene (≥98%, Sigma-Aldrich), 1,4-diiodobenzene (99%, Sigma-Aldrich), acetylacetone (98%, Sigma-Aldrich), 3-hydroxy-4-nitrobenzaldehyde (97%, Sigma-Aldrich), 1,5-diiodopentane (97%, Sigma-Aldrich), and diethylene glycol di(*p*-toluenesulfonate) (98%, Sigma-Aldrich) were used as received. Pyrrolidine (99.5%, Alfa) was purified by fractional distillation from KOH.

Instrumentation. NMR spectra were recorded on a Bruker AC-400 spectrometer in appropriate deuterated solvents. Molar masses were determined by size exclusion chromatography (SEC) at 25 °C, in THF as the eluent (1 mL/min) and with trichlorobenzene as a flow marker, using both refractometric (RI) and UV detectors (Varian). Analyses were performed using a three-column set of TSK gel TOSOH (G4000, G3000, G2000 with pore sizes of 20, 75, and 200 Å respectively, connected in series) calibrated with polystyrene standards. Size exclusion chromatography (SEC) analyses were also performed in DMF at 80 °C with 1g/L LiBr and a flow rate of 0.8 mL/min. The setup consisted of a PL-GPC 50 Plus integrated GPC (Polymer Laboratories, Varian) with a series of three PLgel 5 μm MIXED-D columns. The elution of the filtered samples was monitored using simultaneous UV and refractive index detectors. The elution times were converted to molar mass using a calibration curve based on low dispersity (M_w/M_n) polystyrene standards. Toluene was used as a flow-marker. Differential scanning calorimetry (DSC) measurements were performed on a DSC Q100 apparatus from TA Instruments. Data were recorded during the second run for temperatures ranging from 20 to 200 °C at a heating rate of 10 °C min^{-1}. The cooling rate between the first and second runs was also equal to 10 °C min^{-1}. The glass transition temperature (T_g) was determined by taking the inflection point of the transition. Thermogravimetric analysis (TGA) analyses were performed on a TA Instruments TGA-Q500, under N_2 atmosphere at a heating rate of 5 °C/min.

*Synthesis of Benzyl 4-Formylbenzoate (**2b**).* To a dispersion of 4-formylbenzoic acid (2 g, 13.3 mmol) in a 10/1 MeOH/water mixture (67 mL) was added a 20% aq. Cs_2CO_3 solution up to pH = 8. The resulting solution was stirred at 25 °C for 20 min and concentrated to dryness under vacuum. The residue was dried under vacuum at 60 °C and treated with benzyl bromide (2.4 mL, 20 mmol) in DMF (30 mL). The slurry was stirred under argon at 25 °C for 18 h. The reaction mixture was diluted with a saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with EtOAc (50 mL). The organic layer was then separated and washed again with a saturated aqueous $NaHCO_3$ solution (30 mL), then treated with brine (30 mL), dried with Na_2SO_4, filtered and the organic solvent evaporated. The residue was chromatographed on silica gel (petroleum ether/EtOAc, 9/1 to 7/3) to afford **2b** a white solid (2.5 g, 78%). R_f = 0.38 (petroleum ether/EtOAc, 9/1); mp =147−148 °C. IR (KBr), ν_{max}: 3377, 2964, 2845, 2744, 1719, 1704, 1577, 1501, 1453, 1370 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 10.10 (s, 1H), 8.28−8.19 (m, 2H), 7.99−7.90 (m, 2H), 7.50−7.33 (m, 5H), 5.40 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 191.71, 165.50, 139.34, 135.66, 135.21, 130.42, 129.62, 128.81, 128.62, 128.46, 67.44. HRMS (ESI) $[M + Na]^+$ $C_{15}H_{12}O_3Na$: calculated, 263.06841; found, 263.0681.

*Synthesis of 1,1′-(1,3-Phenylenebis(methylene))bis(piperidin-4-one) (**5**).* To a suspension of 4-piperidone hydrochloride (4.03 g, 26.04 mmol) in a 30/1 CH_2Cl_2/MeOH mixture (124 mL) in a round-bottom flask equipped with a magnetic stirrer, were successively added K_2CO_3 (7,2 g, 52.08 mmol) and 1,3-bis(bromomethyl)benzene (3.44 g, 13.02 mmol). The reaction mixture was stirred at room temperature for 48h, and water (150 mL) was added. After separation, the organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and the organic solvent evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 100/0 to 95/5) to afford **5** as a white solid. (3.91 g, quantitative yield). IR (KBr), ν_{max}: 2959, 2912, 2812, 2769, 1714 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.36−7.24 (m, 4H), 3.63 (s, 4H), 2.75 (t, J = 6.0 Hz, 8H), 2.46 (t, J = 6.0 Hz, 8H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 209.3, 138.4, 129.4, 128.5, 128.0, 62.0, 53.0, 41.4. IR (KBr), ν_{max}: 2959, 2912, 2812, 2769, 1714 cm^{-1}.

*Synthesis of 1,1′-(1,4-Phenylenebis(methylene))bis(piperidin-4-one) (**6**).* The same protocol was used for the synthesis of 1,1′-(1,3-phenylenebis(methylene))bis(piperidin-4-one) (**6**). The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 97/3), affording a white solid (3.63 g, 71%). Analytical data matched those reported in the literature.[50] R_f = 0.34 (CH_2Cl_2/MeOH, 95/5), ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.32 (s, 4H), 3.61 (s, 4H), 2.75 (t, J = 6.1 Hz, 8H), 2.46 (t, J = 6.1 Hz, 8H).

*Synthesis of 1,1′-(1,4-Phenylene)bis(propan-2-one) (**7**).* A procedure reported in the literature was followed,[51,52] and analytical data matched those reported.

*Synthesis of 1,4-Phenylenebis(methylene) Bis(4-formylbenzoate) (**9**).* To a suspension of NaH (160.0 mg, 6.6 mmol) in anhydrous DMF (15 mL) was slowly added a solution of 4-formylbenzoic acid (1g, 6.66 mmol) in anhydrous DMF (5 mL), at 0 °C under argon, and the reaction mixture was stirred for 15 min at 0 °C. A solution of 1,4-

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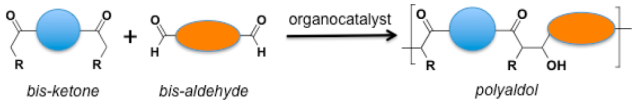
Table 1. Screening of Catalysts and Reaction Conditions for the Polyaldolization at 25 °C between Bis(ketone)s and Bis(aldehyde)s



entry	bis(ketone)	bis(aldehyde)	[M] (mol/L)[a]	catalyst (0.3 equiv)	AcOH (equiv)	time (h)	solvent	$\bar{M}_{n(THF)}$ (g/mol)[b]	$\bar{M}_{w(THF)}$ (g/mol)[b]	D^b	$\bar{M}_{n(DMF)}$ (g/mol)[d]	$\bar{M}_{w(DMF)}$ (g/mol)[d]	D^d
1	**5**	**9**	0.5	A–E	none	120	THF	oligomers[c]	–	–	–	–	–
2	**5**	**9**	0.5	F	none	72	THF	2360	3570 (3600[e])	1.51	6700	12 900	1.9
3	**5**	**9**	0.5	F	1.5	72	THF	2570	4330 (5400[e])	1.68	7800	20 400	2.6
4	**5**	**9**	1	F	1.5	72	THF[i]	2860	5460 (8050[e])	1.90	11 100	54 700	4.9
5	**5**	–	1	F	1.5	240	THF	oligomers[c]	–	–	–	–	–
6	**5**	**9**	1	F	1.5	48	DMSO[i]	–	–	–	15 000	117 000	7.7
7	**5**	**9**	1	F	1.5	48	DMF[i]	–	–	–	15 400	118 600	7.7
8	**5**	**9**	1	F	1.5	48	CH_2Cl_2[i]	–	–	–	11 900	54 700	4.6
9	**5**	**9**	1	F	1.5	48	Toluene[f]	–	–	–	8800	24 900	2.9
10[g]	**5**	**9**	1	F	1.5	18	THF[i]	–	–	–	14 300	103 000	7.2
11[g]	**5**	**11**	1	F	1.5	72	THF[i]	–	–	–	17 000	145 000	8.5
12[g]	**6**	**9**	1	F	1.5	18	THF[i]	–	–	–	14 700	105 400	7.19
13[g,h]	7	**9**	1	F	1.5	18	THF	–	–	–	7600	23 500	3.11
14[g]	**8**	**9**	1	F	1.5	72	THF	oligomers[c]	–	–	–	–	–
15[g]	**5**	**10**	1	F	1.5	72	THF	oligomers[c]	–	–	–	–	–

[a]Concentration of monomers. [b]Molecular weights and dispersity of precipitated polymers as determined by SEC in THF (calibration using polystyrenes as standards). [c]Only oligomers were formed. [d]Molecular weight and dispersity of precipitated polymer were determined by SEC in DMF (calibration using polystyrenes as standards). [e]Molecular weights correspond to first peaks observed by SEC. [f]Polymer was precipitated after 5 min of reaction; the yield was 50%. [g]Pyrrolidine was distilled over KOH. [h]Gelation occurred at the end of the polymerization. [i]A 55–60% yield was obtained.

bis(bromomethyl)benzene (586 mg, 2.22 mmol) in anhydrous DMF (5 mL) was slowly added. The reaction mixture was stirred at 0 °C for 10 min, and then at 60 °C for 12h. A 1 M HCl solution (30 mL) was then added. The aqueous layer was extracted with EtOAc (3 × 90 mL) and the organic layers were washed with a saturated aqueous solution of KCl (2 × 30 mL), and then with a 1 M NaOH solution (2 × 30 mL), dried over Na_2SO_4, filtered, and the solvents evaporated in vacuum. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 100/0 to 90/10), yielding **9** as a white solid (681 mg, 76%). R_f = 0.72 (petroleum ether/EtOAc, 1/1); mp =169–170 °C. IR (neat), ν_{max}: 2947, 2847, 2746, 1708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 10.10 (s, 2H), 8.23 (d, J = 8.2 Hz, 4H), 7.97–7.92 (m, 4H), 7.50 (s, 4H), 5.41 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 191.7, 165.4, 139.4, 136.0, 135.1, 130.4, 129.6, 128.8, 67.0. HRMS (ESI) $[M + Na]^+$ $C_{24}H_{18}O_6Na$: calcd, 425.1001; found, 425.1002.

*Synthesis of 3,3′-Pentane-1,5-diylbis(oxy))bis(4-nitrobenzaldehyde) (**10**).* To a solution of 3-hydroxy-4-nitrobenzaldehyde (500 mg, 2.99 mmol) in DMF (12 mL) were added 1,5-diiodopentane (223 μL, 1.5 mmol) and K_2CO_3 (1.24 g, 8.98 mmol). The reaction mixture was heated to 80 °C under N_2 for 15 h, and the mixture was quenched with a 1 M HCl solution (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL) and the organic layers were washed with a saturated aqueous $NaHCO_3$ solution (3 × 15 mL), then with water (2 × 15 mL) and brine (2 × 15 mL), dried over Na_2SO_4, filtrated, and the solvents evaporated in vacuum. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 8/2 to 1/1), affording **10** as a white solid (189 mg, 31%). R_f = 0.29 (petroleum ether/EtOAc, 7/3); mp =128–129 °C. IR (neat), ν_{max}: 2958, 1703, 1609, 1527, 1288, 1171, 1018, 842, 790 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 10.04 (s, 2H), 7.90 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 1.4 Hz, 2H), 7.52 (dd, J = 8.1, 1.5 Hz, 2H), 4.23 (t, J = 6.1 Hz, 4H), 2.02–1.88 (m, 4H), 1.80–1.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 190.45, 152.55, 143.60, 139.75, 125.97, 122.44, 113.73, 69.85, 28.44, 22.53, HRMS (ESI) $[M + Na]^+$ $C_{19}H_{18}N_2O_8Na$: calcd, 425.0955; found, 425.0937.

*Synthesis of 3,3′-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(4-nitrobenzaldehyde) (**11**).* To a solution of 3-hydroxy-4-nitrobenzaldehyde (2.50 g, 15.00 mmol) in DMF (60 mL) were added oxybis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (3.10 g, 7.48 mmol) and K_2CO_3 (6.21 g, 44.88 mmol). The reaction mixture was heated to 80 °C under N_2 for 15h, and quenched with a 1 M HCl solution (60 mL). The aqueous layer was extracted with EtOAc (3 × 60 mL) and the organic layers were washed with a saturated aqueous $NaHCO_3$ solution (3 × 60 mL), then with water (2 × 60 mL) and brine (2 × 60 mL) dried over Na_2SO_4, filtered, and the solvents evaporated in vacuum. The crude product was purified by flash chromatography ($CHCl_3$/EtOAc, 9/1), producing **11** as a light yellow solid (2.20 g, 73%). R_f = 0.16 (petroleum ether/EtOAc, 7/3); mp =97–98 °C, IR (neat), ν_{max}: 1705, 1607, 1523, 1291, 1277 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 10.04 (s, 2H), 7.90 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 1.4 Hz, 2H), 7.52 (dd, J = 8.1 Hz, 1.5 Hz, 2H, H5), 4.23 (t, J = 6.1 Hz, 4H), 2.02–1.88 (m, 4H), 1.80–1.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 190.5, 152.6, 143.6, 139.7, 126.0, 122.4, 113.7, 69.8, 28.4, 22.5, HRMS (ESI) $[M + Na]^+$ $C_{19}H_{18}N_2O_8Na$: calcd, 425.0955; found, 425.0937.

*Synthesis of 1-Benzyl-3-(hydroxy(4-nitrophenyl)methyl)piperidin-4-one **3a** by Aldol Reaction from **1** and **2a**.* A typical aldol reaction utilizing stoichiometric amounts of substrates **1** and **2a** and pyrrolidine as catalyst is as follows. To a solution of 4-nitrobenzaldehyde (**2a**) (400 mg, 2.64 mmol) in THF were added 1-benzylpiperidin-4-one (**1**) (490 μL, 2.642 mmol) and pyrrolidine (52 μL, 0.528 mmol). The resulting solution was heated to 40 °C for six days, then quenched with a saturated NH_4Cl solution (40 mL) and DCM (50 mL) was added. The aqueous layer was extracted with DCM (2 × 50 mL) and the organic layers were washed with brine (60 mL) dried over Na_2SO_4, filtrated, and the solvents evaporated under vacuum. The crude material was purified by flash chromatography (DCM/EtOAc, 9/1) to afford the desired product **3a** as a yellow oil (270 mg, 30%). R_f = 0.32 (DCM/EtOAc, 9/1). IR (neat), ν_{max}: 3369, 2960, 2868, 1712, 1518, 1344 cm^{-1}. ^1H NMR (300 MHz, THF-d_8), δ (ppm): 8.24–8.01 (m, 2H), 7.60–7.44 (m, 2H), 7.36–7.14 (m, 5H), 5.32 (d, J = 3.8 Hz, 0.5H), 5.25 (d, J = 7.0 Hz, 1H), 3.66 (dd, J = 14.5, 7.0 Hz, 1H), 3.42 (dd, J = 13.0, 2.8 Hz, 1H), 2.93–2.29 (m, 7H). ^{13}C NMR (75 MHz, THF-d_8), δ (ppm): 207.52, 152.58, 151.33, 148.00, 147.77, 139.15, 139.03, 129.73, 129.51, 128.91, 128.82, 128.20, 127.89, 127.75, 127.70,

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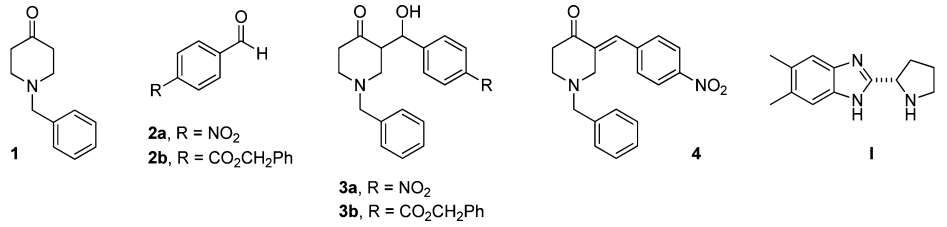

Figure 1. Monofunctional ketone and aldehyde models used for aldol reaction, and structure of the BIP catalyst.

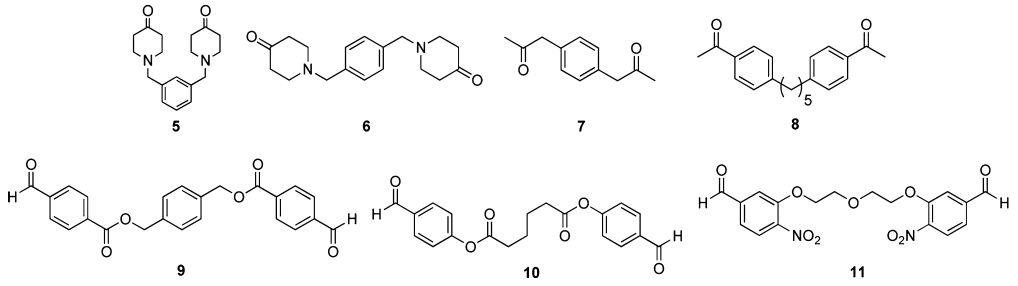

Figure 2. Bis(ketone)s and bis(aldehyde)s investigated in this work.

123.57, 72.66, 70.62, 62.44, 62.42, 58.32, 56.97, 56.20, 54.23, 53.87, 53.33, 41.61, 41.28. HRMS (ESI) $[M + H]^+$ $C_{19}H_{21}N_2O_4$: calcd, 341.1501; found, 341.1491. The crotonization reaction product **4**, namely, 1-benzyl-3-(4-nitrobenzylidene)piperidin-4-one, formed under these conditions. R_f = 0.76 (DCM/EtOAc:9/1); mp =167−168 °C. IR (neat), ν_{max}: 2956, 2913, 2849, 1687, 1600, 1515, 1343 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.29−8.20 (m, 2H), 7.57 (s, 1H), 7.54−7.41 (m, 3H), 7.40−7.24 (m,7H), 3.79−3.68 (m, 4H), 2.98−2.85 (m, 2H), 2.77−2.66 (m, 2H). ^{13}C NMR (75 MHz, THF-d_8), δ (ppm): 196.64, 148.45, 142.52, 139.19, 137.80, 132.25, 131.78, 129.57, 129.04, 127.98, 124.24, 62.85, 56.39, 50.62, 39.89. HRMS (ESI) $[M + H]^+$ $C_{19}H_{19}N_2O_3$: calcd, 323.1396; found, 323.1396.

General Polymerization Procedure (See Table 1). To a solution of bis(ketone) at 0.25 mol/L in the selected solvent was added 30 mol % of catalyst in the presence or the absence of 150 mol % of acetic acid. After 10 min of stirring, a stoichiometric amount of the bis(aldehyde) (0.25 mol/L) was added. After a given time, the polymer was purified by two consecutive precipitations in 10-fold excess of diethyl ether to eliminate catalyst, unreacted monomers and oligomers. After filtration, the polymers were dried under vacuum and obtained as white solids. In a typical experiment, polymerization of bis-piperidinone **5** and bis(aldehyde) **9** was carried out as follows (entry 10 in Table 1). 1,1′-(1,3-Phenylenebis(methylene))bis(piperidin-4-one) (**5**) (80 mg, 0.25 mmol) was dissolved in 0.5 mL of THF. Pyrrolidine (6 μL, 30 mol %) and acetic acid (21 μL, 150 mol %) were then added. After the solution was stirred for 10 min at room temperature, 1,4-phenylenebis(methylene) bis(4-formylbenzoate) (**9**) (100 mg, 0.25 mmol) was added. The initial suspension turns to a clear and yellow solution after the reaction started. After 3 days of reaction at 25 °C, the crude solution was analyzed by ^1H NMR (THF-d_8) to determine the conversion (85%), and the solution was precipitated twice in diethyl ether. The polymer was obtained as a white solid (100 mg, 60%). M_w = 103 000 g/mol, D = 7.2 analyzed in SEC DMF (UV detector).

Another typical polymerization experiment of bis(piperidinone) **5** and bis(aldehyde) **11** was as follows (entry 11, Table 1). 1,1′-(1,3-Phenylenebis(methylene))bis(piperidin-4-one) (**5**) (80 mg, 0.25 mmol) was dissolved in THF (0.5 mL). Pyrrolidine (6 μL, 30 mol %) and acetic acid (21 μL, 150 mol %) were added. After stirring the solution for 10 min at room temperature, 3,3′-((oxybis(ethane-2,1-diyl))bis(oxy))bis(4-nitrobenzaldehyde) (**11**) (101 mg, 0.25 mmol) was added. After 3 days of reaction at 25 °C, the crude solution was analyzed by ^1H NMR (THF-d_8) to determine the conversion (82%), and the solution was precipitated twice in diethyl ether and the resulting polymer was obtained as a white solid (100 mg, 55%). M_w = 145 000 g/mol, D = 8.5 analyzed in SEC DMF (UV detector). Results of the other polymerization experiments are provided in Table 1.

RESULTS AND DISCUSSION

While a large excess of ketone and quite a high loading in catalyst (30 mol %) are generally employed for the aldol reaction in molecular chemistry,[4,19,21] polyaldol synthesis by step-growth polymerization requires antagonist bifunctional monomers employed at stoichiometry. In addition, the aldehyde should not self-dimerize (or self-polymerize) under the reaction conditions, hence it should preferably be nonenolizable. Aldehydes carrying electron withdrawing groups such as $-NO_2$ or an ester group are expected to exhibit an enhanced reactivity as electrophilic partners. In contrast, the nucleophilic ketone should be enolizable, but its reaction by self-condensation should also be avoided. Finally, further dehydration of the aldol product under the reaction conditions, forming C═C double bonds, has also to be taken into account. On the basis of our previous investigations,[53] preliminary studies on catalyzed aldol reactions were carried out using benzimidazole-pyrrolidine (BIP) (**I**, Figure 1), using stoichiometric amounts of ketones and aldehydes. Ketone **1** and aldehydes **2a**,**b**, in line with the above requirements, were selected as suitable candidates for model reactions. The aldol process between equimolar amounts of **1** and **2a** and **2b**, in the presence of 10 mol % of BIP and 20 mol % of trifluoroacetic acid, effectively afforded corresponding aldol products **3a**,**b** in satisfying yields, albeit with modest diastereoselectivity (see Supporting Information), along with the crotonization product **4**. Although leading to partial dehydration in one case, these model reactions constituted encouraging results for an extension of the aldol reaction to polymer synthesis. In order to avoid any complication with further determination of enantiomeric purity of the resulting polymers, it was envisioned to test the aldolization reaction using pyrrolidine, a simpler analogue of BIP. On the basis of the above results, the reaction involving stoichiometric amounts of monofunctional model reagents **1** and **2a** in the presence of a catalytic amount of pyrrolidine was tested (see Experimental Section). The targeted aldol product **3a** was obtained, though formation of the

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crotonized product **4** (by water elimination) was also noted under these conditions.

On the basis of these premises, extension of the model reactions to the polyaldolization was then carried out using a selection of bis(ketone)s and bis(aldehyde)s, as shown in Figure 2. Thus, *N*-substituted bis-piperidinones, such as **5** or **6**, were selected over bis-cyclohexanones as potential monomers, the latter substrates featuring two asymmetric carbon atoms, which would result in a complex NMR analysis of related polyaldols.

Both the bis(piperidinone) **5** and the bis(aldehyde) **9** were first selected as reaction partners for a screening of polyaldolization reaction conditions at room temperature. Considering preliminary results obtained with BIP and pyrrolidine, various cyclic and acyclic secondary and tertiary amines were tested as organic catalysts for repeated aldol reactions (Figure 3; see also Table 1). The aldolization mechanism catalyzed by a secondary amine, forming iminium and enamine intermediates is depicted in Scheme 1.

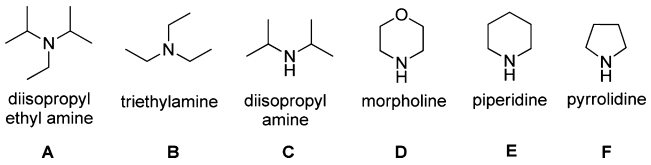
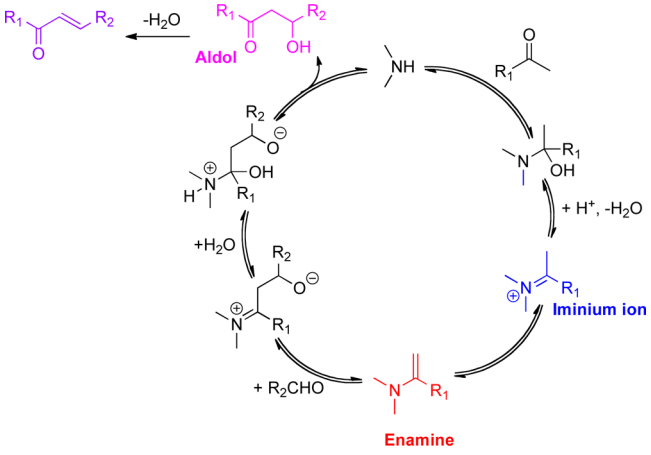


Figure 3. Secondary and tertiary amine catalysts investigated in this work.

Scheme 1. Secondary Amine–Catalytic Cycle of Direct Aldolization (from the Iminium to the Enamine, a Proton Is Generated)



Acyclic secondary amines, such as diisopropylamine, and tertiary amines such as triethylamine and diisopropylethylamine proved inefficient to promote crossed polyalolization, even after 5 days at room temperature. Similarly, six-membered ring cyclic secondary amines such morpholine and piperidine did not show any noticeable catalytic activity, in spite of the well-known ability of cyclic secondary amines to catalyze the aldol reaction via enamine or iminium type activation (Scheme 1).[4] In contrast, the closely related five-membered ring cyclic secondary amine, namely, pyrrolidine was found to be catalytically active, though a rather high loading of 30 mol % relative to monomers was needed. The nucleophilicity of pyrrolidine originates from the ability of the nitrogen center to donate electrons, decreasing ring strain, a feature which is less present in other cyclic amines including cyclohexylamine or morpholine.[54] Under such conditions, polymers with an apparent weight-average molecular weights M_w = 12 900 g/mol and a dispersity ($D = M_w/M_n$) of 1.9 (SEC in DMF, relative to PS standards, entry 2, Table 1) could be obtained after 3 days at room temperature. SEC traces of polymers synthesized in this way showed multimodal distributions (Figure 4) typical of a step-growth polyaddition process.

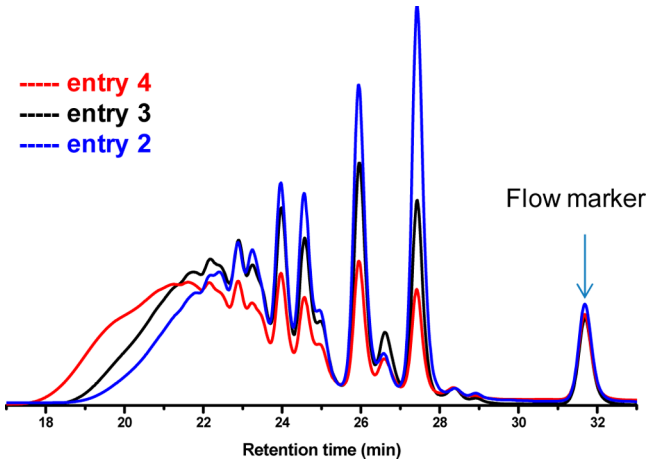


Figure 4. SEC traces in THF of polymers obtained from the polymerization of bis-piperidone **5** and bis(aldehyde) **9** at 25 °C in THF, in the presence of 30 mol % pyrrolidine (blue curve, entry 2) and [Monomers] = 0.5M; 30 mol % pyrrolidine and 150 mol % acetic acid and [monomers] = 0.5 M (black curve, entry 3); 30 mol % pyrrolidine and 150 mol % acetic acid and [monomers] = 1 M (red curve, entry 4).

Note that apparent molecular weights determined by SEC in THF (also relative to PS standards) were 3–4 times lower compared to values obtained in DMF. It is however highly likely that apparent polymer molecular weights as determined by SEC in DMF are overestimated.

Interestingly, use of acetic acid (AcOH, 150 mol % relative to monomers) allowed increasing the molecular weight at room temperature (entry 3), as also illustrated in Figure 4 (black curve). Such a bifunctional bicomponent catalytic system using pyrrolidine and AcOH in a 1 to 3 molar ratio was previously reported by Barbas et al. for aldol reactions of α,α-dialkylaldehyde donors and arylaldehyde acceptors.[53] The role of acetic acid would be to increase the electrophilicity of carbonyl groups of the bis(ketone), through protonation or H-bonding, thus facilitating the nucleophilic addition of the pyrrolidine and, consequently, the formation of iminium and enamine intermediates (see Scheme 1).[4,55] A significant increase in M_w of the resulting polymers, from 20 400 g/mol (entry 3) to 54 700 g/mol (entry 4), was noted in SEC traces in DMF by simply increasing monomer concentration from 0.5 to 1M. A control experiment showed that bis(ketone) **5** could not undergo self-polyaldolization: only oligomers did form under the crossed polymerization reaction conditions (entry 5, Table 1).

Representative ^{13}C and ^{1}H NMR spectra of a polymer derived from polyaddition of bis-piperidinone **5** and bis(aldehyde) **9** are shown in Figure 5. Formation of aldol monomer units can be evidenced through the presence of characteristic signals f and d at 208.2 and 73.4–71.4 ppm, corresponding to the ketone group and CHOH groups of the

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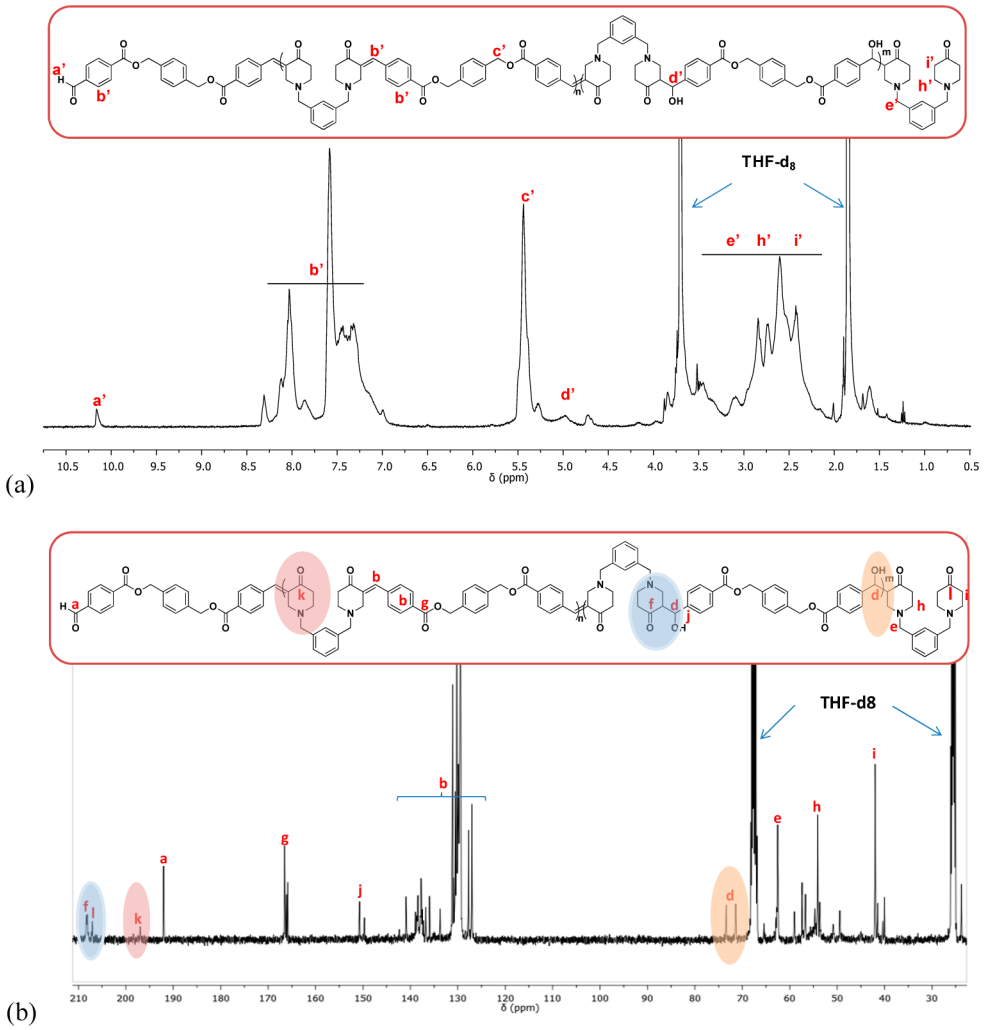


(a)

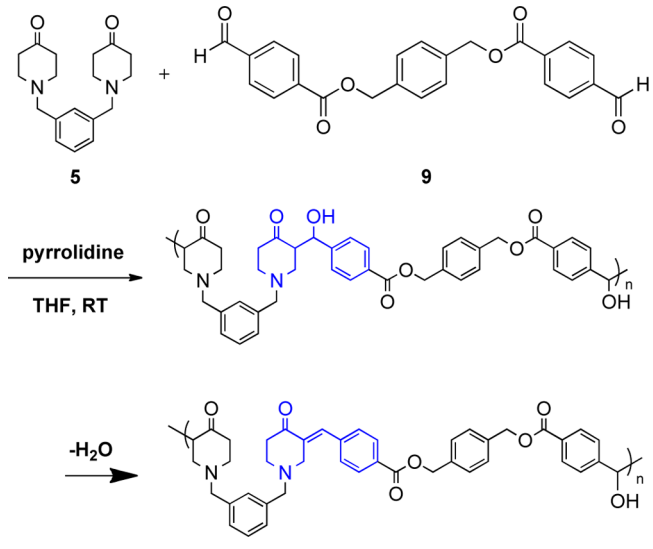
(b)

Figure 5. ^{1}H NMR (a) and ^{13}C NMR (b) spectra (THF-d_8) of compound resulting from the polymerization of bis(piperidinone) **5** and bis(aldehyde) **9** (entry 4, Table 1).

aldol moiety, respectively. The signal g at 166.1 ppm can be assigned to the main-chain ester functions, while the sharp peak at 192.0 ppm is due to the resonance of aldehyde end-groups. Noteworthy is the presence of a further ketone signal (k) at 196.9 ppm, that is, 11 ppm downshifted compared to signal f, which can be assigned to the carbon atom of an α,β-unsaturated ketone. These conjugated double bonds thus arise from partial dehydration (crotonization) of aldol monomer units, the enone moiety being the thermodynamic product, as depicted in Scheme 2.

The splitting of some signals appearing both in the ^{13}C and the ^{1}H NMR spectra are due to the formation of diastereoisomers (e.g., carbon d in Figure 5b) during repeated aldol reactions. Analysis by two-dimensional NMR confirms the presence of these two configurations (Figure S1, Supporting Information). Quantitative analysis by ^{13}C NMR allowed us to roughly determine the extent of crotonization and the presence of α,β-unsaturated ketone double bonds (Figure S2). The percentage was calculated from the intensity of peaks k and f, using the following equation: % of dehydration = $I_k/(I_k + I_f)$, where I is the intensity of corresponding signals. For instance, the polyaldol obtained from monomers **5** and **9** (entry 4, Table 1) was constituted of ~20% of conjugated double bonds, as a result of the dehydration of parent aldol units.

Scheme 2. Polyaldol Synthesis from Bis(ketone) 5 and Bis(aldehyde) 9 and Subsequent Formation of Vinylene Units Forming the Corresponding Polyaldol by Dehydration under Acidic Conditions



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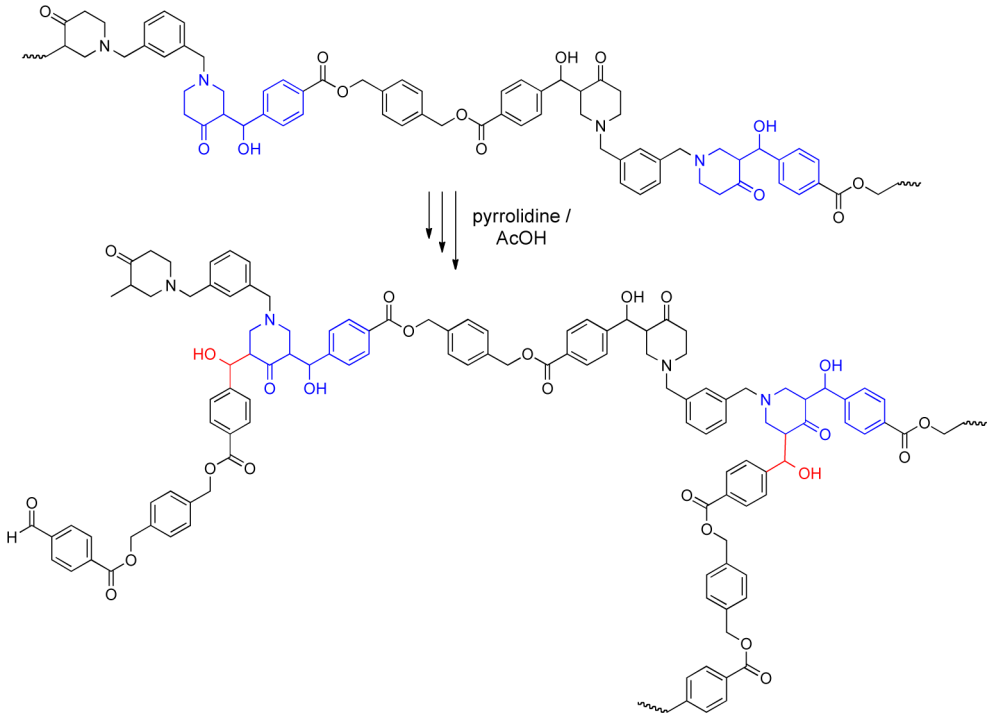
Scheme 3. Branching Formation by Intermolecular Aldol Reactions Involving Aldol Units (Case of the Polyaldol Obtained from Monomers 5 and 9)



Further analysis of the same polyaldol by differential scanning calorimetry (DSC) indicated that this polymer was amorphous, with a glass transition temperature (T_g) of 32.9 °C after the second heating cycle (Figure S3). Thermogravimetric analysis (TGA) showed an initial weight loss of the polymer at 100 °C presumably due to dehydration of aldol monomer units, and further degradation continuing up to 900 °C (Figure S4).

We next noticed that purifying pyrrolidine by distillation prior to use led to higher apparent mass-average molecular weights: M_w from 54 700 g/mol to 103 000 g/mol by SEC in DMF, relatively to PS standards (entry 10, see also Figure S5). This can be attributed to the presence of residual water and/or carbonation of crude pyrrolidine, hampering optimal reactivity of the secondary amino function. Analysis by quantitative ^{13}C NMR of the corresponding polyaldol revealed the formation of up to 33% of vinylene units generated by dehydration (Figure S6). Hence, a catalytic system consisting of purified pyrrolidine in conjunction with acetic acid provided a higher polyaldolization rate, but also favored subsequent dehydration of aldol units.

Solvent effect on the polymerization of bis(piperidinone) **5** and bis(aldehyde) **9** was also studied. DMSO, DMF and DCM were all found suitable polyaldolization solvents, similar M_w values being observed by SEC (entries 6−8, Table 1) under otherwise identical experimental conditions. In contrast, toluene led to a lower M_w value (24 900 g/mol, entry 9), likely due to the poor solubility of the resulting polyaldol. However, polar solvents such as DMF and DMSO also led to polyaldols with a significantly higher molecular weigh distribution. We hypothesized that this could be ascribed to subsequent intermolecular aldolization reactions leading to branched polymers, thus increasing the polyaldol dispersity (Scheme 3). Ultimately, cross-linking could be observed under forcing conditions and/or with specific monomers (see further).

To extend the scope of the pyrrolidine/acetic acid-induced polyaldolization reaction, different combinations of bis(aldehyde)s and bis(ketone)s were tested, using the following optimized conditions: 30 mol % purified pyrrolidine in the presence of 150 mol % acetic acid, 1 M monomer concentration, in THF at 25 °C. Not surprisingly, the 1,3-bis(piperidinone) **5** could be polymerized smoothly with the more reactive bis(nitroaldehyde) **11**, leading, within 12 h, to a polyaldol with an apparent M_w value of 145 000 g/mol (entry 11). A quite high dispersity was also observed in this case (D = 8.5), presumably due to the incidence of intermolecular reactions between aldol monomer units discussed above. Similarly, the isomeric 1,4-bis(piperidinone) monomer **6** could be polymerized with bis(aldehyde) **9** (entry 12), affording the corresponding polyaldol with an average molecular weight of 105 400 g/mol and a dispersity of D = 7.19 within 18 h. The quantitative ^{13}C NMR analysis of the latter polymer indicated formation of up to 25% of dehydrated aldol units (Figure S7). The *p*-substituted bis(ketone) **7** was also found suitable to engage in polyaldolization with bis(aldehyde) **9**, although lower average molecular weight was obtained (M_w = 23 500 g/mol, D = 3.11; entry 13). In the latter case, prolonged reaction time led to gel formation (formation of an insoluble polymer) which may be the result of competitive intermolecular couplings of polymer chains. The presence of even more acidic protons in the aldol units arising from **7**, in comparison to **5**, may favor these aldol reactions leading, ultimately, to a 3D cross-linked polymer (see Scheme S1). Further studies are needed to confirm this hypothesis.

In contrast, reaction between the commercial bis-acetophenone **8** and the bis(aldehyde) **9** yielded only oligomers (entry 14), even after a reaction time of 3 days. This was consistent with the fact that acetophenone (not shown), which can viewed as the monofunctional analogue of **8**, did not form any aldol when reacted with *p*-nitrobenzaldehyde **2**. Finally, polymer-

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ization of the bis-piperidinone **5** with the bis(aldehyde) **10** (entry 15) also resulted in the production of oligomers, even after prolonged reaction time (up to 3 days). In this case, the lower reactivity of the bis(aldehyde) **10** might be ascribed to the presence of a deactivating mesomeric donor oxygen atom in *para* position of the aldehyde function.

CONCLUSIONS

Bis(ketone) and bis(aldehyde) monomers can be directly polymerized under stoichiometric conditions by a crossed step-growth polyaldolization process, affording unprecedented organosoluble poly(β-ketoalcohol)s referred to as polyaldols. N-substituted bis(piperidinone)s are nucleophilic and enolizable monomers of choice that can efficiently react with nonenolizable bis(aldehyde)s, the reactivity of which can be enhanced by incorporating electron withdrawing groups, such as nitro or ester groups. Such a monomer design allows selectively driving the polymerization toward direct aldol-type polymers, without the occurrence of the self-polymerization of the bis(aldehyde) or the bis(ketone) under the experimental conditions examined in this work. Triggering these polymerizations by an organocatalyic pathway utilizing pyrrolidine in conjunction with acetic acid produces polyaldols exhibiting a multimodal molecular weight distribution that is characteristic of a step-growth polymerization. A subtle change of the catalyst structure has a dramatic impact on the molecular features of the obtained polyaldols. Moreover, polar solvents such as DMF or DMSO or prolonged reaction time in THF can significantly broaden the molecular weight distribution of polyaldols, owing to branchings occurring by competitive intermolecular aldol reactions involving monomer units. Monomer concentration is also momentous, formation of insoluble cross-linked polyaldols being triggered by a too high monomer concentration.

Polyaldols can also undergo partial dehydration forming conjugated ketone units whose extent depends on the experimental conditions and the structure of the parent polymer. This feature could be further exploited to achieve π-conjugated polymers arising from complete dehydration of polyaldols grown by the metal-free synthetic approach developed in the present work. This study, along with preliminary results on aldol reactions with the homochiral BIP catalyst, also open avenues to design chiral polyaldols through the use of chiral catalysts via asymmetric polymerization. It is foreseen that the transfer of chirality from the catalyst to the prochiral centers would occur at each aldol reaction step. It might be expected that physicochemical properties of related chiral polyaldols be different than those of racemic counterparts.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures for the reaction of **1** and **2a,b**, catalyzed by BIP, 2D and quantitative ^{13}C NMR spectra, SEC, DSC, TGA analyses of some polyaldols, and a scheme showing further aldol reactions from polyaldols leading to gel formation. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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