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ETHYLENE/VINYL ACETATE-BASED MACROCYCLES VIA ORGANOMETALLIC-MEDIATED RADICAL POLYMERIZATION AND CUAAC 'CLICK' REACTION

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Recent advances in organometallic-mediated radical polymerization led to unique α,ω-difunctional poly(vinyl acetate) (PVAc) and ethylene/vinyl acetate copolymers (EVA). A copper-catalyzed Huisgen dipolar cycloaddition ring-closure reaction was applied to these difunctional precursors paving the way to unprecedented PVAc and/or EVA macrocycles, and to their PVOH- and EVOH-counterparts after hydrolysis.

The past decade has witnessed huge progress in the design of copolymers with controlled molecular parameters, compositions and also topologies including notably linear, branched or star polymers. In particular, considerable efforts have been made to develop efficient synthetic routes towards cyclic structures. Nowadays, these macrocycles are no longer considered as a curiosity and have demonstrated distinct bulk and solution properties as compared to their linear analogs such as increased glass transition temperature, lower hydrodynamic volume, higher thermostability, *etc*.[1–3,4] Synthesis methods for cyclic polymers (*c*-polymers) are numerous and fall into two main categories, *i.e.* 'ring-expansion' and 'ring-closure' techniques.[4,5] The former almost exclusively concerns *c*-polymers formed *via* ring-opening polymerization (ROP).[6] In contrast, the 'ring-closure' approach,[6] implying the cyclisation of a linear polymer, notably *via* 'click reactions', is more versatile but depends on the availability of the corresponding difunctional linear precursors. In this respect, progress in living/controlled polymerizations constantly offers new perspectives for the preparation of novel macrocyclic structures.

In particular, controlled radical polymerization (CRP) constitutes a straightforward strategy for the preparation of difunctional (co)polymers used as precursors of macrocycles.[7] For example, the cyclisation of α,ω-thiol polystyrene (PS), produced by sequential reversible addition fragmentation chain transfer (RAFT) followed by the conversion of the dithioester end groups into thiols, was achieved by disulfide bond formation under diluted conditions.[8,9] As another illustration, α,ω-bromobenzyl-terminated PS formed by atom transfer radical polymerization (ATRP) were subjected to allylation reaction followed by ring-closing metathesis in the presence of a Grubbs' 2nd generation catalyst.[10] Some heterodifunctional linear polymers produced by CRP also served as macrocycle precursors. Indeed, cyclic PS was obtained by the intramolecular copper-catalyzed Huisgen dipolar cycloaddition (CuAAc) reaction of an α-alkyne-ω-azido-terminated PS prepared by ATRP[11–17] or RAFT.[18] The same strategy was applied to the ring-closure of polyacrylates[19,20] and thermoresponsive poly-*N*-isopropylacrylamide (PNIPAM)[21,22] precursors. A series of polymers (PS, PNIPAM, poly(*tert*-

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butyl acrylate) (PtBA), and poly(*N*,*N*-dimethylacrylamide (PDMA)), bearing a thiol at one extremity and an acrylate group at the other chain end were preformed by RAFT and cyclized in one-pot using a thiol–ene reaction.[23] The intramolecular Diels–Alder reaction applied to an α-maleimide-ω-cyclopentadienyl functionalized PtBA and poly(methyl methacrylate), synthesized *via* ATRP, also yielded the desired cycles in high purity.[24]

As illustrated by the above mentioned examples, the very large majority of cyclic polymers derived from CRP are produced from conjugated monomers. Despite the importance of polymers derived from unconjugated vinyl monomers, also called 'less activated monomers' (LAMs), including poly(vinyl ester)s, poly(*N*-vinylamide)s or ethylene-containing copolymers like ethylene/vinyl acetate copolymers (EVA), examples of macrocycles based on LAMs are scarce. This limitation mainly originates from the difficulty in producing difunctional linear LAM-based precursors with high chain end fidelity. To our knowledge, only the group of Zhang reported a successful synthesis of poly(vinylacetate) (PVAc) and poly(*N*-vinylpyrrolidone) (PNVP) macrocycles.[25] Typically, linear heterodifunctional polymers bearing cyclopropenone-masked dibenzocyclooctyne and azide end groups were prepared by RAFT before cyclisation by a light-induced strain promoted azide–alkyne cycloaddition (SPAAC) reaction under highly diluted conditions.

Herein, we developed a novel strategy for the synthesis of unique LAM-based macrocycles, including PVAc and/or EVA-containing cycles. For this purpose, we took advantage of the latest progress in the field of organometallic-mediated radical polymerization (OMRP),[26] well-known for its ability to control the polymerization of LAMs, especially VAc and ethylene/VAc.[26–29] Our general strategy, represented in Scheme 1, consists of four steps. Briefly, the OMRP of LAMs was initiated from an halomethyl organocobalt(iii) complex[30] (i) followed by radical dimerization of the polymers *via* cobalt-mediated radical coupling (CMRC)[31] upon treatment with isoprene (ii) leading to α,ω-dibromo polymers. Subsequent conversion of the terminal bromides into azido groups (iii) and CuAAc reaction of the resulting α,ω-azide-terminated polymers with 1,6-heptadiyne used as a difunctional coupling agent (iv) produced the targeted PVAc or EVA-containing cyclic structures. Note that the same cyclisation strategy was applied to a PVAc-*b*-EVA-*b*-PVAc triblock precursor for preparing the corresponding *c*-PVAc-*b*-EVA macrocycle. Ultimately, the hydrolysis of the ester functions of these unique structures was also considered leading to macrocycles composed of PVOH and/or EVOH sequences (Scheme 1, v).

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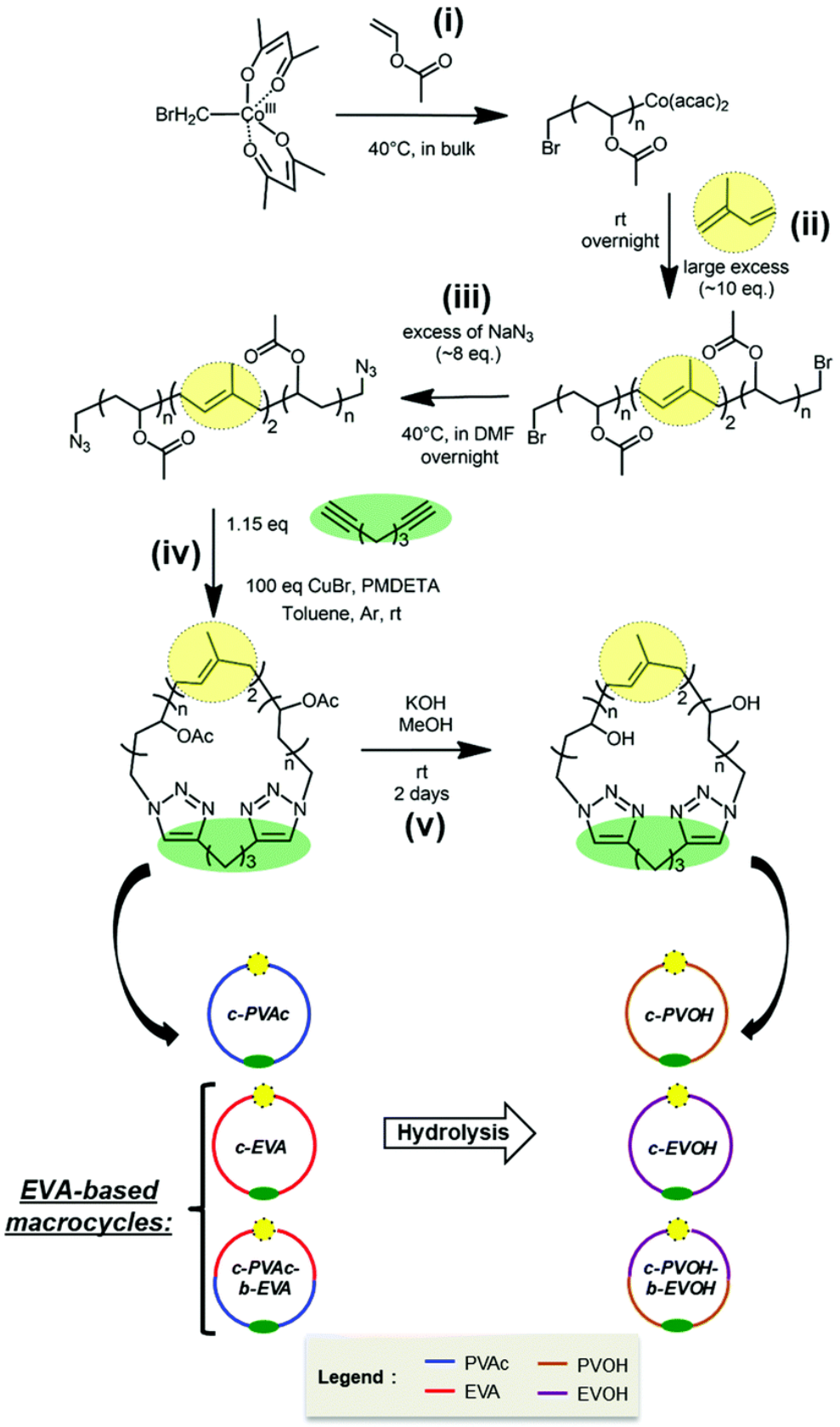

Scheme 1. General strategy for the synthesis of PVAc and/or EVA-containing macrocycles and their hydrolyzed counterparts.

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First, we prepared the α-bromo functional polymer chains by OMRP (i) and converted them in one pot into the corresponding α,ω-dibromo linear precursor *via* CMRC (ii) (Scheme 1). More precisely, the OMRP of VAc was initiated at 40 °C in bulk from a bis-(acetylacetonato) organocobalt(iii) complex bearing a bromomethyl function, *i.e.* $BrCH_2$-$Co(acac)_2$. The synthesis of this complex was described recently as well as its ability to control the polymerization of VAc under these conditions.[30] Upon heating, the rupture of the C–Co bond occurred generating a bromomethyl radical, which initiated the radical polymerization of VAc. Along the polymerization, the reversible capping of the growing radical chains by $Co(acac)_2$ ensured the control of the process. Starting from a $[VAc]_0/[BrCH_2$-$Co(acac)_2]_0$ ratio of 121, after 9 h, the conversion reached 18% leading to an α-bromo-PVAc-$Co(acac)_2$ with low dispersity (M_n = 3000 g mol^{-1}, M_p = 3370 g mol^{-1}, $Đ$ = 1.17) (Table 1, entry 1). At this stage, isoprene (about 20 eq. as compared to Co) was added into the polymerization medium in order to promote the radical coupling of the chains and to produce the α,ω-dibromo-PVAc (Br-PVAc-Br) (Scheme 1, ii). SEC analysis revealed a monomodal peak with an almost perfect doubling of the molar mass (M_n = 6640 g mol^{-1}, M_p = 7770 g mol^{-1} $Đ$ = 1.14) compared to the PVAc precursor suggesting its quantitative coupling (Fig. S1A†). As expected, ^{1}H NMR analysis of the coupled product showed a typical signal at 3.3 ppm corresponding to the bromomethyl (Br$C\underline{H}_2$–) functions (Fig. S2†). A degree of polymerization (DP) of 77 ($M_{n\,NMR}$ = 6620 g mol^{-1}) was determined based on the relative intensities of signals of Br$C\underline{H}_2$– and –$C\underline{H}$OAc of the repeating units (at 4.8 ppm). This value is fully consistent with the one obtained by SEC supporting a very high level of functionalization of the Br-PVAc-Br chains. Structures of the α-bromo PVAc precursor and of the α,ω-dibromo PVAc resulting from CMRC were also confirmed by MALDI mass spectrometry (Fig. S3†). In agreement with the CMRC mechanism,[32] various populations differing by the number of inserted isoprene units (y = 2–5) were detected in the mass spectrum of the α,ω-dibromo PVAc (Fig. S3B†).

Table 1. Synthesis of α-bromo and α,ω-dibrominated polymers by OMRP and CMRC

		α-Bromo OMRP product			α,ω-Bromo CMRC product			
Entry	Polym	M_n[a] (g mol^{-1})	M_p[a] (g mol^{-1})	$Đ$[a]	M_n[a] (g mol^{-1})	M_p[a] (g mol^{-1})	$Đ$[a]	$F_{ethylene}$ of EVA[b]
1	Br-PVAc-Co^{III}	3000	3370	1.17	6440	7770	1.14	—
2	Br-EVA-Co^{III}	2510	3800	1.32	6600	8060	1.17	0.59
3	Br-PVAc-*b*-EVA-Co^{III}	1780	2240	1.22	3470	5040	1.28	0.54

Polymerization and coupling conditions are detailed in the Experimental section. a Determined by SEC-THF calibration. b Calculated with the copolymer composition from ^{1}H NMR.

In a similar approach, we prepared α,ω-dibromo EVA and PVAc-*b*-EVA-*b*-PVAc copolymers. The organometallic-mediated radical copolymerization of VAc and ethylene was initiated by $BrCH_2$-$Co(acac)_2$ at 40 °C in bulk under 50 bar of ethylene pressure. After 14% of VAc conversion, the reactor was vented before the addition of isoprene leading to a low dispersity difunctional Br-EVA-Br (M_n = 6600 g mol^{-1}, $Đ$ = 1.17) containing 59% of ethylene (Table 1, entry 2). On the other hand, the sequential OMRP of VAc (conversion = 12%) followed by the pressurization of ethylene (E) at 50 bar and VAc/E copolymerization (total VAc conversion = 22%) led to Br-PVAc-*b*-EVA-Co^{III} (Table 1, entry 3). Further isoprene-assisted radical coupling reaction of the latter produced a telechelic Br-PVAc-*b*-EVA-*b*-PVAc-Br triblock copolymer having two external PVAc blocks of 1170 g mol^{-1} and one internal EVA sequence of 1220 g mol^{-1} characterized by an ethylene molar fraction ($F_{ethylene}$) of 0.54.

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Before considering any CuAAc cyclisation, it was necessary to substitute the bromide functions of the above mentioned telechelic (co)polymers with azide moieties (Scheme 1, iii). In this respect, Br-PVAc-Br was reacted with an excess of sodium azide in DMF at 40 °C overnight. The substitution of bromide functions at both chain ends and the formation of N_3-PVAc-N_3 were evidenced by ^{1}H NMR and FT-IR spectroscopy (Fig. S2 and S4†) as well as by mass spectrometry (Fig. 1). ^{1}H NMR signals corresponding to the terminal methylene –CH_2X (X being either –Br or –N_3) shifted from 3.37 to 3.34 ppm upon substitution of bromides by azides (Fig. S2†). As evidenced by mass spectrometry, different α,ω-diazide PVAc populations containing various numbers of isoprene units (y = 2–5) in their backbone were identified (Fig. 1). For instance, a theoretical model for a polymer with 56 VAc units and 2 isoprene units was simulated and is presented in Fig. 1(b). The azide moieties were easily detected by FT-IR with the appearance of a characteristic signal of the –N_3 stretch band at 2090 cm^{-1} (Fig. S4†). A suitable post-modification of the Br-EVA-Br and Br-PVAc-*b*-EVA-*b*-PVAc-Br and the formation of their azide-functionalized counterparts were also confirmed by ^{1}H NMR and FT-IR spectroscopy (Fig. S2 and S4†).

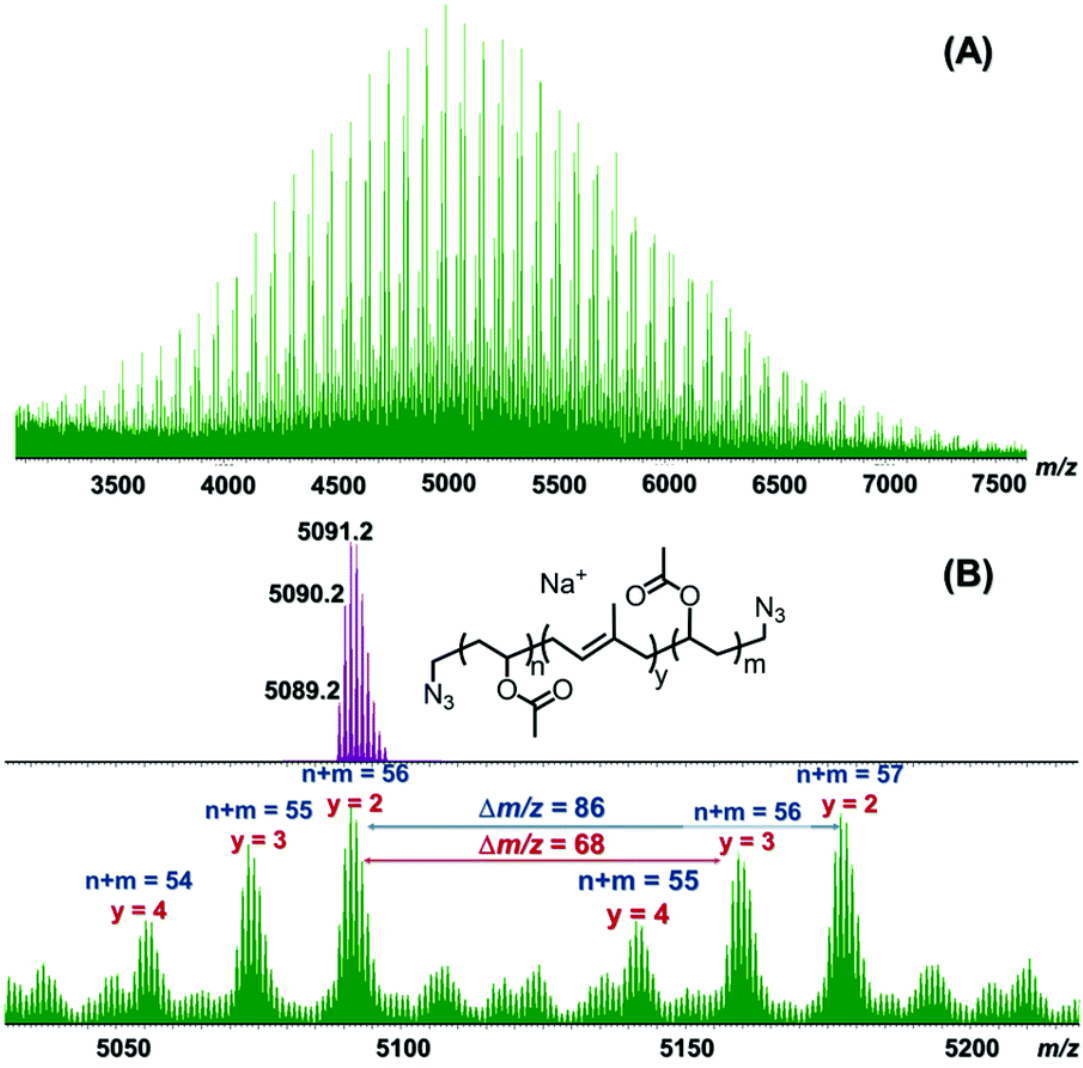

Fig. 1. MALDI mass spectrum of N_3-PVAc-N_3: (A) global mass spectrum and (B) magnification between m/z 5010 and m/z 5240 and comparison with theoretical model.

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In the cyclisation step (Scheme 1, iv), the linear α,ω-diazide precursors were reacted with a dialkyne compound, *i.e.* 1,6-heptadiyne, in the presence of copper bromide (CuBr) and *N*,*N*,*N*',*N*''-pentamethyldiethylenetriamine (PMDETA), which catalyzed the CuAAC 'click' reaction leading to triazole functions (green circles in Scheme 1). Such a bimolecular ring-closure approach involving a telechelic polymer and a difunctional coupling agent occurs in two steps: the reaction of one chain end of the polymer with one complementary functional group of the coupling agent followed by an intramolecular reaction between the residual polymer chain end and functionality on the coupling agent. This approach is known to be sensitive to the stoichiometry of the reactant. Indeed, it is reported that excess or deficit of coupling agent as compared to the telechelic polymer significantly affects the cyclisation yield.[4] In the former case, the reaction of the polymer with two different coupling agents prevents the intramolecular cyclisation whereas intermolecular reaction, and possibly oligomerization, occurs when a default of coupling agent is used.[6] Inspired by previously reported procedures,[3,4,33–35] as a first trial, we added a solution containing stoichiometric amounts of linear N_3-PVAc-N_3 and 1,6-heptadiyne in toluene at a slow rate (0.3 mL h^{-1}) at rt within a highly diluted CuBr/PMDETA solution in toluene (2.4×10^{-3} M) (Table 2, entry 1). High dilution and slow addition of the reactants were implemented in order to limit the local concentration of the species and favor the intramolecular cyclisation rather than the intermolecular polyaddition. After complete addition of the reactants, the medium was stirred for 24 h before analyzing the products. SEC analysis of the polymer after a click reaction revealed a multimodal distribution (Fig. 2A). The latter is composed of a main population (62% upon deconvolution) having a lower apparent molar mass (higher elution volume) as compared to the precursor. This population corresponds to the targeted cyclic PVAc (*c*-PVAc) as anticipated by the reduction in the hydrodynamic volume associated with the cyclisation.[4] Importantly, no decrease of the molar mass of the polymer was observed upon mass spectrometry. At variance, the middle of the distribution is slightly shifted toward higher molecular weight due to the addition of the dialkyne (Fig. 3A). Therefore, we can unambiguously conclude that the increase in the SEC elution volume after CuAAc results from the reduction of the hydrodynamic volume of the polymer following the cyclisation process and not from the degradation of the backbone. Although the combination of MS and SEC results confirmed effective ring closure, a difference of 2 mass units (u) was observed when comparing the theoretical and experimental isotopic distribution for the sodiated *c*-PVAc (Fig. 3B). The formation of one unsaturation within the molecule might account for such a discrepancy but, at this stage, we have no evidence supporting this hypothesis. Besides the desired cyclic product, SEC traces also showed a minor population with a higher apparent molar mass compared to the precursor (Fig. 2A), resulting from intermolecular polyaddition reactions. Given the difficulty in reaching perfect equimolarity due to the imprecision (about 10%) in the ^{1}H NMR integration of the chain-end and taking into account the above-mentioned considerations on the origin of the possible oligomerization in the bimolecular ring-closure approach,[6] we slightly increased the amount of heptadiyne in the second assay in order to decrease the contamination of *c*-PVAc (Table 2, entry 2). Moreover, when increasing the amount of diyne in the medium (Table 2, entry 2), the probability of the formation of dialkyne-terminated chains should be higher as well as the risk of formation of higher molar mass side products *via* Glaser coupling.[36] The latter consists of a Cu^{II}-catalyzed coupling reaction between two alkyne end-chains.[36] For this reason, inspired by the

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work of Koberstein *et al.*,[36] before any purification treatment of the macrocycles, we added $Sn(Oct)_2$ in the crude mixture. It is expected to reduce Cu^{II} possibly generated from Cu^{I} exposed to oxygen (Table 2, entry 2), and thus to avoid any Glaser coupling side reaction. Overall, under these conditions, the extent of the higher molar mass population could be minimized and the yield of *c*-PVAc increased to 74% (Table 2, entry 2 and Fig. 2B).

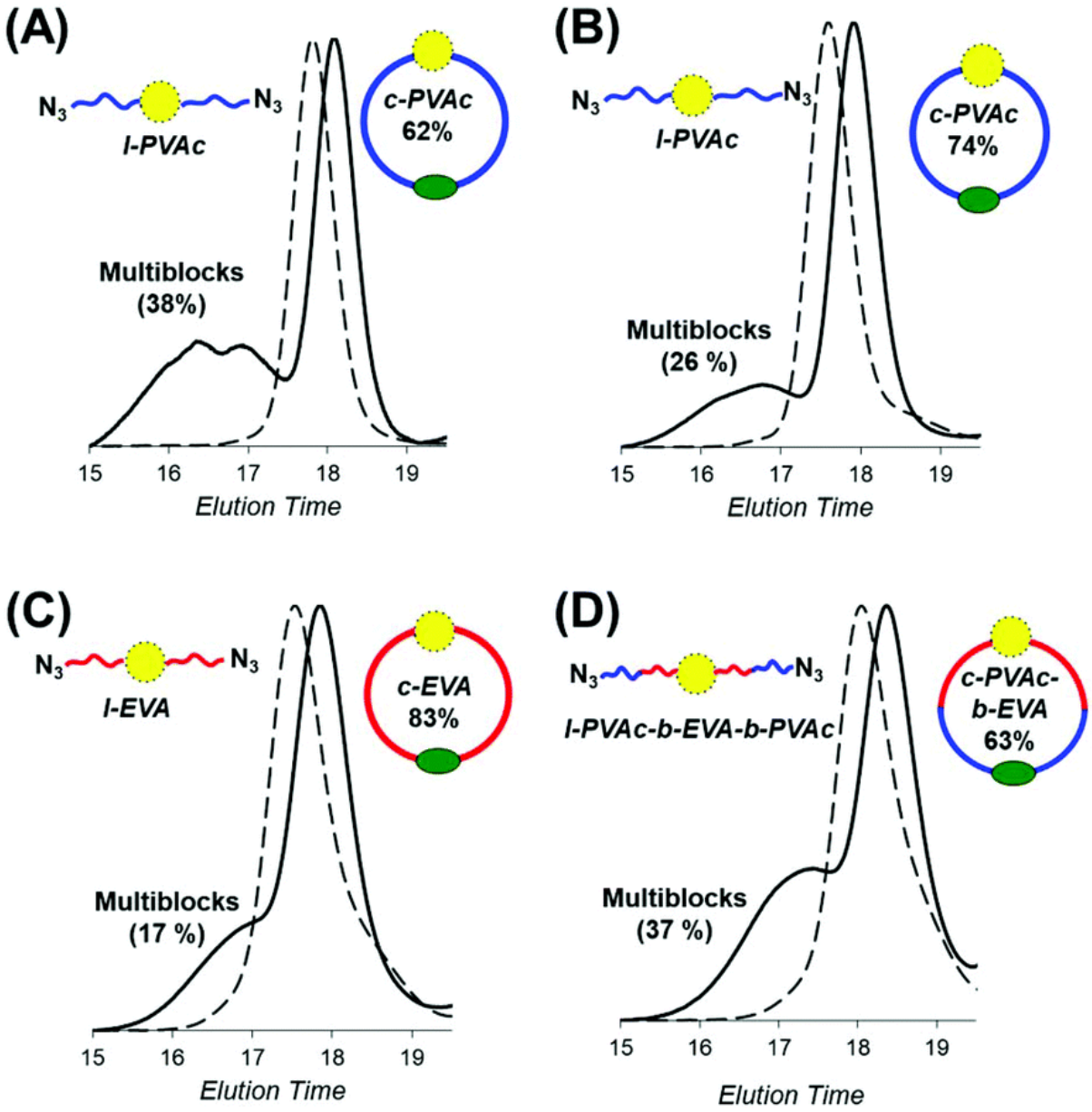

Fig. 2. Size-exclusion chromatography traces of linear (- - -) and cyclic (—) PVAc (A and B, Table 2 entries 1 and 2, respectively), EVA (C, Table 2 entry 3) and PVAc-*b*-EVA-*b*-PVAc (D, Table 2 entry 4).

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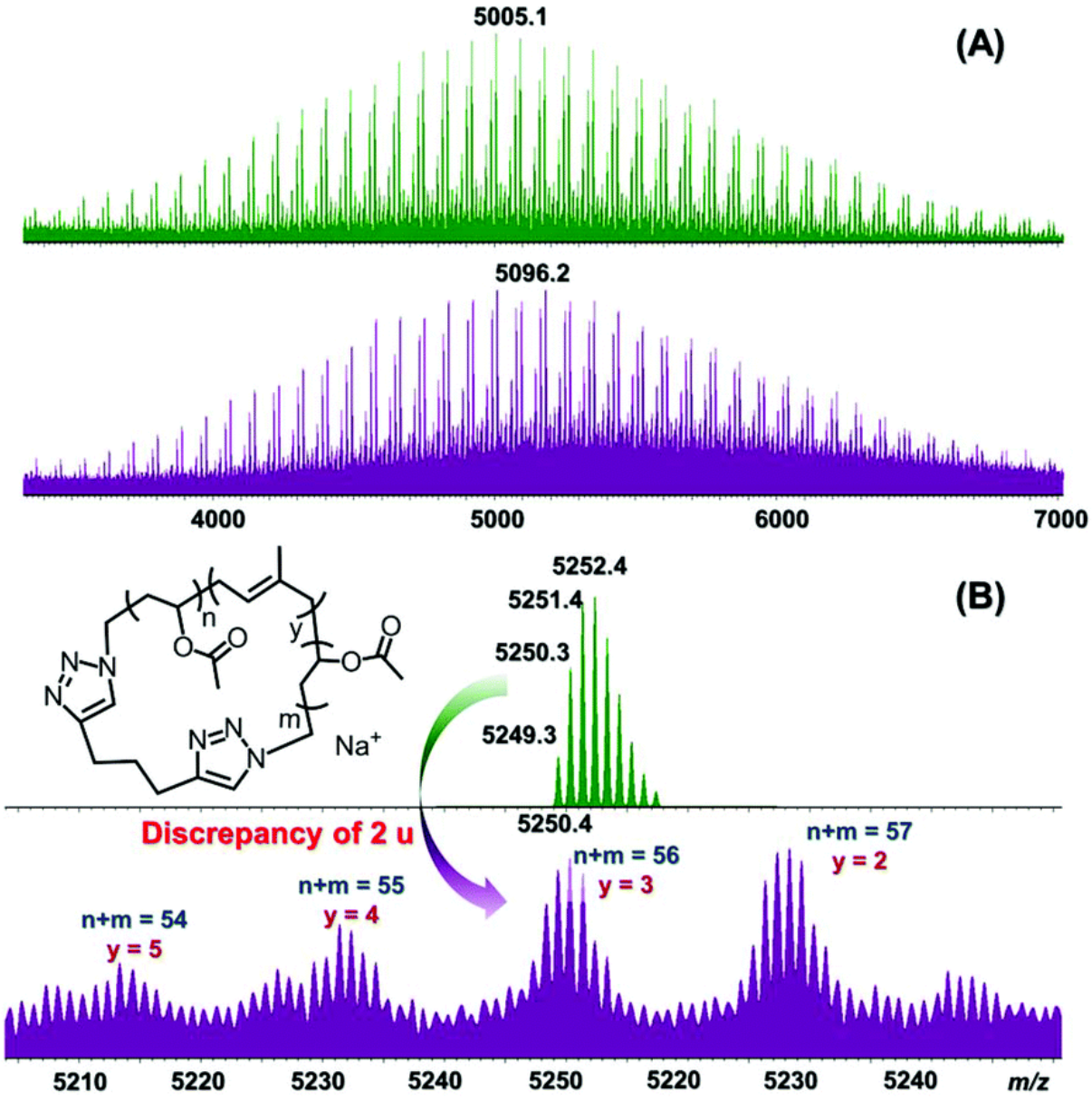

Fig. 3. MALDI mass spectra: (A) comparison between N_3-PVAc-N_3 (green) and cyclic PVAc (purple), (B) magnification between *m/z* 5200 and *m/z* 5260 for cyclic PVAc and comparison with theoretical model.

Table 2. Copper(i)-catalyzed alkyne–azide cyclisation

		Precursor			Cyclic product		
Entry	Polym	M_n[c] (g mol^{-1})	M_p[c] (g mol^{-1})	$Đ$[c]	[1,6-Heptadiyne]/[N_3-P-N_3]	M_p[c] (g mol^{-1})	Cyclic[d] (%)
1[a]	N_3-PVAc-N_3	6650	7030	1.06	1.00	5640	62
2[b]	N_3-PVAc-N_3	6660	7900	1.13	1.19	6130	74
3[b]	N_3-EVA-N_3	6380	8270	1.21	1.25	6450	83
4[b]	N_3-(PVAc-*b*-EVA_2	4060	5480	1.26	1.18	4210	63

Cyclisation conditions: Details are in the Experimental part (ESI), [PMDETA] = [CuBr] = 2.4×10^{-3} M, flow rate: 0.3 mL h^{-1} at room temperature. a The cyclic PVAc has been exposed to air, dried by rotavapor and purified from the major part of copper salts using Cuprisorb in THF. b The cyclic polymer has been purified *via* column chromatography under Ar after the addition of 2 eq. of $Sn(Oct)_2$ as compared to CuBr. c Determined by SEC-THF calibration PS. d Calculated from the areas of the convoluted SEC peaks.

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Applying this cyclisation strategy to the N_3-EVA-N_3 precursor gave access to EVA macrocycles for the very first time. The yield of *c*-EVA reached up to 83% (Table 2 entry 3 and Fig. 2C), suggesting a high level of chain end functionality of the precursor combined with a quite efficient cyclisation reaction. Next, we considered the preparation of unique macrocycles composed of one PVAc segment and one EVA block *via* cyclisation of the N_3-PVAc-*b*-EVA-*b*-PVAc-N_3 triblock (Table 2, entry 4). This challenging *c*-PVAc-*b*-EVA was formed in a 63% yield (Fig. 2D). This moderate yield probably results for the lower chain end fidelity of the linear multiblock precursor whose synthesis relies on a higher number of steps. Nevertheless, the combination of OMRP and CuAAC paved the way to the formation of unprecedented ethylene-containing multiblock macrocycles.

Finally, the ester moieties of these macrocycles were hydrolyzed in order to give access to the corresponding cyclic structures composed of poly(vinyl alcohol) (PVOH) and/or ethylene vinyl alcohol (EVOH). According to a well-described procedure,[37] *c*-PVAc was treated overnight by KOH in degassed methanol at 40 °C. The FT-IR spectra in Fig. 4 confirmed the conversion of *c*-PVAc into the *c*-PVOH counterpart, as indicated by the disappearance of the carbonyl band at 1730 cm^{-1} and the appearance of a broad band at 3300 cm^{-1}. A similar procedure was applied to the cyclic EVA-containing copolymers except that the latter were solubilized in toluene prior to the dropwise addition of KOH/MeOH. Again, the hydrolysis of the acetate groups was complete leading to the corresponding *c*-EVOH and *c*-PVOH-*b*-EVOH (Fig. 4).

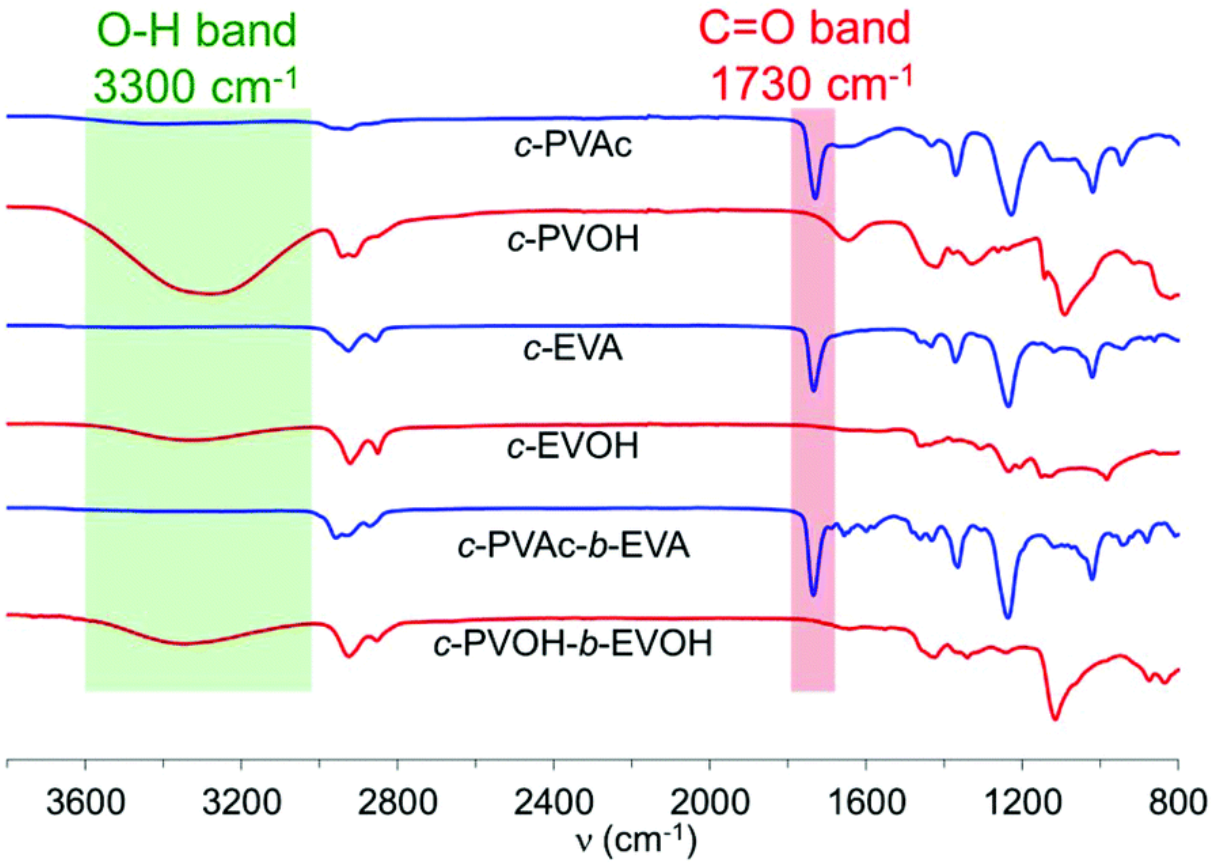

Fig. 4. FT-IR spectra of PVAc and/or EVA containing macrocycles before and after hydrolysis.

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Conflicts of interest

There are no conflicts to declare.

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