Tagging alcohols with cyclic carbonate: a versatile equivalent of (meth)acrylate for ring-opening polymerization†

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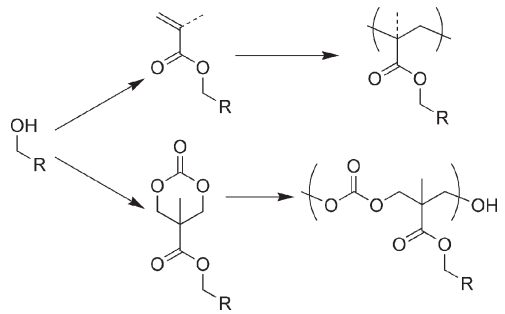
Received (in Berkeley, CA, USA) 11th September 2007, Accepted 11th October 2007
First published as an Advance Article on the web 25th October 2007
DOI: 10.1039/b713925j

Cyclic carbonate monomers based on a single biocompatible scaffold allow for incorporation of a wide range of functional groups into macromolecules *via* ring-opening polymerization.

Acrylic and methacrylic polymers are ubiquitous in modern applications due to the wide variety of properties that can be introduced by variation of the pendant groups. The wide variety of commercially available monomers, coupled with recent advances in controlled radical polymerization techniques, have enabled the generation of new classes of well-defined functional macromolecules. In comparison, the inventory of cyclic ester and carbonate monomers available and suitable for ring-opening polymerization (ROP) is more limited. Methods have been developed for the synthesis of functional lactones[1–5] and cyclic carbonates[6] but there is as yet no widely adapted method for incorporating arbitrary functional groups into these ROP monomers.

To provide a more versatile and accessible library of ROP monomers, we have exploited recently developed organocatalytic methods for ROP of cyclic carbonate monomers derived from 2,2-bis(methylol)propionic acid (bis-MPA). Bis-MPA has proven a versatile building block for the construction of biocompatible dendrimers.[7] The syntheses of carbonate monomers derived from bis-MPA typically employ acetonide protection–deprotection schemes prior to installation of the pendant functional group prior to forming the cyclic carbonate moiety.[8] Our approach involves the synthesis of the cyclic carbonate **1** as a versatile synthon for a family of functionalized carbonated monomers. This synthetic scheme parallels the powerful approach of (meth)acrylate derivatization as a means of creating monomers (Scheme 1).

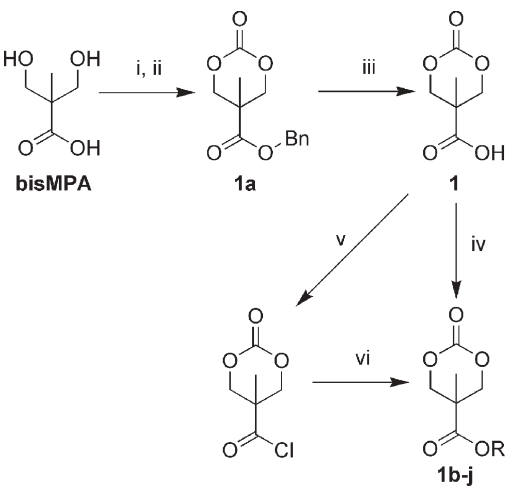
The synthesis of **1** can easily be carried out on a 0.1 mol scale (16 g) with typical laboratory apparatus following the procedures outlined in Scheme 2.[9] Two procedures for the coupling of **1** to alcohols were used: either direct coupling using DCC, or conversion to the acyl chloride using oxalyl chloride followed by reaction with the alcohol or amine in the presence of base. The latter method has the advantage that the salt byproducts are easily removed. Compared to methods wherein the functional group is attached prior to carbonate formation, the inverse sequence described here more generally requires only a single unique reaction and purification step for new pendant groups. Using these methods, a range of functional groups could be incorporated to generate new ROP monomers offering opportunities for couplings



Scheme 1 Derivatization of alcohols with (meth)acrylate for radical polymerization (top) compared with cyclic carbonate for ring-opening polymerization (bottom).

via substitution, cycloaddition, and amide or disulfide linkages, or for introducing strongly hydrophilic or hydrophobic groups (Scheme 3).

To test the suitability of these bis-MPA-derived monomers for polymerization, we examined the organocatalytic ROP of monomer **1a** bearing a simple benzyl group for comparison to the archetypical carbonate monomer, trimethylene carbonate (TMC).[10] As summarized in Table 1, both the two-component catalyst consisting of the Lewis acid 1-(3,5-bis(trifluoromethyl)-phenyl)-3-cyclohexyl-2-thiourea (TU) with the Lewis base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or alternatively the superba-



Scheme 2 Synthesis of **1**-type monomers from bis-MPA. Conditions: (i) BnBr, KOH, DMF, 100 °C, 15 h, 62%. (ii) Triphosgene, pyridine, CH_2Cl_2, −78 → 0 °C, 95%. (iii) Pd/C (10%), H_2 (3 atm), EtOAc, RT, 24 h, 99%. (iv) ROH, DCC, THF, RT, 16 h. (v) $(COCl)_2$, THF, RT, 1 h, 99%. (vi) ROH, NEt_3, RT, 3 h.

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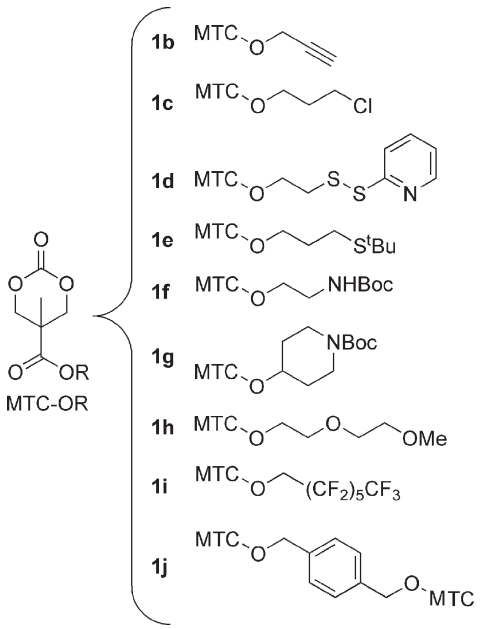
† Electronic supplementary information (ESI) available: Synthetic details and characterization for **1b**–**1j** monomers. See DOI: 10.1039/b713925j



Scheme 3 Monomers synthesized *via* procedures in Scheme 2.

sic catalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) showed high conversions of **1a** to polymer in relatively short times. Good control over the molecular weight and polydispersity was achieved with the TU–DBU co-catalyst, while TBD is more active and its use leads to broadening of the polydispersity *via* transcarbonation of the polymer chains. No scrambling of the pendant benzyl ester into the poly(**1a**) chains could be observed using ^{1}H-NMR spectroscopy. While excessively bulky substituents (*e.g.* 2,2-diphenyl) impede the ring-opening of six-membered cyclic carbonates,[8a,11] the increased rate of polymerization for **1a** when compared to TMC indicates that the methyl and carboxylate substituents are well-suited for polymerization. The location of steric bulk distant from the polymerizing carbonate also avoids interference with the organocatalysts; substituents in the α-position of cyclic ester monomers dramatically reduce the rates of polymerization when organocatalysts are used, making them incompatible with effective derivatization strategies using α-chloro and α-azido groups.

Random copolymerizations of the cyclic carbonates with TMC were conducted using organocatalytic procedures similar to those for the homopolymerizations of TMC and **1a** described above (Table 2). Monitoring experiments (^{1}H NMR spectroscopy) reveal that all of the **1b**–**1i** comonomer was incorporated into polymer within 1 h, while the conversion of TMC lagged and did not reach >90% conversions until after 3 h. The relative reactivities match the higher reactivity found for **1a** *vs.* TMC in homopolymerization, and suggest that gradient copolymers are formed. The observation that these polymerizations continue on after complete consumption of the faster-reacting monomer contrasts with behavior we have observed for random copolymerizations of lactones, in which the faster reacting monomer reacts exclusively under organocatalytic conditions.[12] Block copolymers of different carbonate repeat units can also be constructed by sequential polymerization: for instance, following *in situ* formation of a PTMC macroinitiator (conditions as per Table 1; $[M]_0/[I]_0$ = 37.5, TU–DBU, 3 h; 86% conversion, M_n = 5900, PDI = 1.03), monomer **1a** was added to the reaction solution, and after 30 min the chain-extended polymer was obtained (conversion = 92% (TMC), 88% (**1a**); M_n = 9700, PDI = 1.08).

Table 1 Organocatalytic polymerizations of **1a** *vs.* TMC

Monomer[a]	Catalyst[b]	Time/h	Conv.[c] (%)	M_n[d]/g mol^{-1}	M_w/M_n[d]
1a	TU–DBU	0.5	93	11 600	1.12
	TU–DBU	1	94	11 500	1.15
	TU–DBU	2	95	12 900	1.20
	TBD	5 min	95	13 200	1.52
	TBD	1	96	8000	1.76
TMC	TU–DBU	1	45	4400	1.03
	TU–DBU	2	74	7300	1.03
	TU–DBU	3	90	8600	1.03
	TBD	5 min	98	8900	1.08
	TBD	1	98	11 000	1.31

[a] Conditions: 1 M monomer in CH_2Cl_2 with 0.02 M PyBuOH, 20 °C. [b] TU–DBU: both 0.05 M; TBD: 0.01 M. [c] By ^{1}H NMR spectroscopy. [d] By GPC *vs.* polystyrene standards, uncorrected.

Table 2 Random copolymerizations of TMC with **1**-derived monomers

Comonomer[a]	Time/h	Conversion TMC[b] (%)	Conversion comonomer[b] (%)	M_n[c]/ g mol^{-1}	M_w/M_n[c]
1b	1	61	>95	4700	1.10
	4	95	>95	6500	1.11
1g	1	46	>95	3900	1.07
	4	91	>95	5700	1.07
1h	1	49	>95	5300	1.09
	4	92	>95	7800	1.11
1i	1	60	>95	6100	1.05
	4	91	>95	8600	1.05

[a] Conditions: 1 M monomer in CH_2Cl_2, 80 : 20 TMC : comonomer (mol : mol), 0.02 M PyBuOH, 0.05 M TU, 0.05 M DBU, 20 °C. [b] By ^{1}H NMR spectroscopy. [c] By GPC *vs.* polystyrene standards, uncorrected.

In summary, a general synthetic route to incorporate a broad range of functional groups into cyclic carbonate monomers has been developed. These monomers can be polymerized under mild, one-pot conditions to create random or block copolymers. Further studies are underway to complete procedures for full deprotection and derivatization of polar sidegroups once they are incorporated into polymers.

Notes and references

1 T. Mathisen, K. Masus and A.-C. Albertsson, *Macromolecules*, 1989, **22**, 3842; K. Stridsberg and A.-C. Albertsson, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 3407; R. K. Srivastava and A.-C. Albertsson, *J. Polym. Sci., Part A: Polym. Chem.*, 2005, **43**, 4206.

2 M. Trollsås, V. Y. Lee, D. Mecerreyes, P. Löwenhielm, M. Möller, R. D. Miller and J. L. Hedrick, *Macromolecules*, 2000, **33**, 4619.

3 B. Parrish, J. K. Quansah and T. Emrick, *J. Polym. Sci., Part A: Polym. Chem.*, 2002, **40**, 1983; B. Parrish and T. Emrick, *Macromolecules*, 2004, **37**, 5863; B. Parrish, R. B. Breitenkamp and T. Emrick, *J. Am. Chem. Soc.*, 2005, **127**, 7404; B. Parrish and T. Emrick, *Bioconjugate Chem.*, 2007, **18**, 263.

4 R. Riva, S. Schmeits, F. Stoffelbach, C. Jerome, R. Jerome and P. Lecomte, *Chem. Commun.*, 2005, 5334; P. Lecomte, R. Riva, S. Schmeits, J. Rieger, K. Van Butsele, C. Jerome and R. Jerome, *Macromol. Symp.*, 2006, **240**, 157; R. Riva, S. Schmeits, C. Jerome, R. Jerome and P. Lecomte, *Macromolecules*, 2007, **40**, 796; H. Li, R. Riva, R. Jerome and P. Lecomte, *Macromolecules*, 2007, **40**, 824.

5 Y. D. Y. L. Getzler, V. Mahadeven, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 2002, **124**, 1174; V. Mahadevan, Y. D. Y. L. Getzler and G. W. Coates, *Angew. Chem., Int. Ed.*, 2002, **41**, 2781; J. A. R. Schmidt, V. Mahadevan, Y. D. Y. L. Getzler and G. W. Coates, *Org. Lett.*, 2004, **6**, 373; J. A. R. Schmidt, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 2005, **127**, 11426; J. W. Kramer, E. B. Lobkovsky and G. W. Coates, *Org. Lett.*, 2006, **8**, 3709.
6 G. Rokicki, *Prog. Polym. Sci.*, 2000, **25**, 259.
7 H. Ihre, A. Hult and E. Söderlind, *J. Am. Chem. Soc.*, 1996, **118**, 6388; H. Ihre, A. Hult, J. M. J. Fréchet and I. Gitsov, *Macromolecules*, 1998, **31**, 4061; H. Ihre, O. L. Padilla De Jesús and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2001, **123**, 5908; M. Malkoch, E. Malmström and A. Hult, *Macromolecules*, 2002, **35**, 8307; O. L. P. De Jesus, H. R. Ihre, L. Gagne, J. M. J. Fréchet and F. C. Szoka, *Bioconjugate Chem.*, 2002, **13**, 453; E. R. Gillies, E. Dy, J. M. J. Fréchet and F. C. Szoka, *Mol. Pharmacol.*, 2005, **2**, 129; C. C. Lee, E. R. Gillies, M. E. Fox, S. J. Guillaudeau, J. M. J. Fréchet, E. E. Dy and F. C. Szoka, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 16649.
8 (*a*) K. D. Weilandt, H. Keul and H. Höcker, *Macromol. Chem. Phys.*, 1996, **197**, 3851; (*b*) T. F. Al-Azemi and K. S. Bisht, *Macromolecules*, 1999, **32**, 6536; T. F. Al-Azemi, J. P. Harmon and K. S. Bisht, *Biomacromolecules*, 2000, **1**, 493; T. F. Al-Azemi and K. S. Bisht, *Polymer*, 2002, **43**, 2161; B. D. Mullen, C. N. Tang and R. F. Storey, *J. Polym. Sci., Part A: Polym. Chem.*, 2003, **41**, 1978; Z.-L. Liu, Y. Zhou and R.-X. Zhuo, *J. Polym. Sci., Part A: Polym. Chem.*, 2003, **41**, 4001; Y. Zhou, R. Zhuo and Z. Liu, *Polymer*, 2004, **45**, 5459; Y. Zhou, R.-X. Zhuo and Z.-L. Liu, *Macromol. Rapid Commun.*, 2005, **26**, 1309.
9 T. F. Al-Azemi and K. S. Bisht, *J. Polym. Sci., Part A: Polym. Chem.*, 2002, **40**, 1267.
10 F. Nederberg, B. G. G. Lohmeijer, F. Leibfarth, R. C. Pratt, J. Choi, A. P. Dove, R. M. Waymouth and J. L. Hedrick, *Biomacromolecules*, 2007, **8**, 153.
11 T. Hino and T. Endo, *Macromolecules*, 2003, **36**, 5902; H. Keul, R. Bächer and H. Höcker, *Makromol. Chem.*, 1986, **187**, 2579; H. R. Kricheldorf, A. Stricker and M. Lossin, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 2179.
12 R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, R. M. Waymouth and J. L. Hedrick, *J. Am. Chem. Soc.*, 2006, **128**, 4556; B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F. Nederberg, J. Choi, C. Wade, R. M. Waymouth and J. L. Hedrick, *Macromolecules*, 2006, **39**, 8574.

