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Topochemical Polymerization using Bis-thyminyl Monomers

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Topochemical polymerization is one way to synthesize novel macromolecular architectures with stereoregular chain structures. The $[2\pi + 2\pi]$-cycloaddition of certain conjugated diene monomers is one such form of topochemical polymerization. Unfortunately, the design of new monomers that can undergo topochemical $[2\pi + 2\pi]$-polymerization to form linear polymers can be a formidable challenge due to the strict geometrical criteria governing the reactivity of monomer crystals. In this research ten bis-thymine monomers were synthesized, that varied with respect to the N1-functionality, the size of the N3-N3-polyethylene spacer, or the type of rigid N3-N3-aryl spacer employed. On irradiation, five of the crystalline monomers were found to undergo topochemical photo-reactions. The crystal structures of the bis-thymyl monomers were used to investigate the monomer structure-reactivity relationships. The molecular weights of the photo-products were determined and the thermal properties of some of the new materials were also evaluated using thermo analytical techniques.

Introduction

Solid state reactions are increasingly being investigated for their utility in the synthesis of complex molecules with controlled regio- and stereospecificity.\textsuperscript{1} In particular, solid state reactions such as the 1,4-polymerization of diacetylenes and dienes, the 1,6-polymerization of trienes and triacetylenes have afforded a number of interesting linear polymers from thermal or radiation-induced topochemical polymerization.\textsuperscript{2-6} A challenging aspect of these topochemical polymerizations, however, is that the reactive molecules must be suitably positioned/oriented within the crystal lattice in order to generate the desired polymers in high yield.

Among the topochemical reactions mentioned above, the $[2\pi + 2\pi]$-cycloaddition organic reactions has been investigated for the synthesis of a broad range of cyclobutane-containing molecules including ladderanes, cyclophanes and hetero-dimers.\textsuperscript{7-10} However, to date, reports on topochemical polymerization by the cycloaddition are limited.\textsuperscript{11-14}

Thymine, one of the nucleic bases in DNA, exhibits the ability to dimerize by the $[2\pi + 2\pi]$-cycloaddition and bis-thymine derivatives also have the ability to form reversible polymers by photo-polymerization via the $[2\pi + 2\pi]$-cycloaddition of thymine units within the molecules.\textsuperscript{15} However, it is well known that the irradiation of solutions of bis-thymine derivatives does not readily produce polymers.\textsuperscript{16} Instead, appropriate molecular conformation and intermolecular alignments are necessary for photo-polymerization (Fig. 1). Intramolecular photo-dimerization can be achieved when bis-thymine derivatives adopt closed conformation (Fig. 1b), whilst higher molecular weight polymers can only be achieved when the monomers adopt open conformations (Fig. 1a).\textsuperscript{17} Moreover, the monomers must align continuously with respect to one another for polymerization, rather than forming discrete pairs.\textsuperscript{18} Discrete pairs are likely to limit the achievable molecular weights through formation of photo-dimers (Fig. 1c).

Schmidt postulated that reacting olefins must lie parallel with one another and be separated by <4.2 Å.\textsuperscript{19} Therefore for bis-thymine derivatives to successfully photo-polymerise by the $[2\pi + 2\pi]$-cycloaddition mechanism, alignment of the derivatives in the crystal lattice must satisfy all these criteria.

![Figure 1](image-url) (a) Polymerization, (b) Intramolecular cyclisation, (c) Cyclic Dimerisation.
We have investigated the photo-activity of bis-thymine derivatives to form polymers by several methods. Photo-polymerizations of bis-thymine derivatives with a template polymer in the film state, were studied in order to align bis-thymines using hydrogen bonding interactions between the derivatives and template polymer. However, this strategy resulted only in the formation of oligomers from the photoreactions.

We recently succeeded in forming a higher molecular weight polymer from the irradiation of crystalline butyl-linked thyminyl methyl propanoate (dimethyl 3,3'-(3,3'-(butane-1,4-diyi)bis(5-methyl-2,4-dioxo-3,4-dihydropyrimidine-3,1(2H) -diyl)) dipropanoate) via topochemical polymerization. This is the first successful example using thyminyl groups as the polymerization site. However, we only reported this one example and did not present detailed studies concerning the monomer crystal design.

Our recent crystallographic and quantum chemical studies suggested that to achieve desirable π-π stacking of the reactive olefins, bis-thymine monomers should be designed in such a way that: the N3 and N1 nitrogen atoms of thymine in bis-thyminyl monomers are blocked to prevent hydrogen bonding between thymine units; that N1-substituted derivatives should bear functional groups that are less susceptible to disruptive hydrogen bonding interactions (e.g., methyl ester); and that 3 carbon N1 spacers should be used instead of 2 carbon spacers (i.e., propyl instead of ethyl) to permit greater flexibility of the chains and prevent disruptive chain-ring interactions.

In this paper, we report the synthesis and structural characterization of a number of symmetrical bis-thyminyl monomers that are formed by bridging two thyminyl units at the N3 position, and use this information to systematically investigate how simple chemical modifications can influence the crystal packing and photo-reactivity of bis-thymine monomers. Next, solid crystalline polymerizations of selected monomers were undertaken, and the products were characterized using several analytical techniques (NMR, MALDI-TOF-MS, TGA, and DSC).

**Experimental**

**Materials and Methods.** All chemicals were purchased from Sigma-Aldrich, Castle Hill, NSW, Australia. Solvents were purchased from Merck, Kilsyth, Victoria, Australia. Melting points were determined using a Buchi B-545 melting point apparatus with a digital thermometer. Infrared spectra were recorded on a Perkin Elmer 1600 series Fourier Transform infrared spectrometer as KBr disks; or by using a Bruker Equinox 55 in ATR mode with diamond as the background reference. 1H NMR spectra were recorded at 400 MHz on a Bruker DPX-400 spectrometer. 13C NMR spectra were recorded at 100 MHz on a Bruker DPX-400 spectrometer. Electrospray ionisation mass spectra (ESI) were recorded on a Micromass platform II API QMS Electrospray mass spectrometer with cone voltage 10 V, 25 V or 35 V. Analyses was performed in positive (ESI+) and negative mode (ESI-). The molecular weight of irradiated samples was determined by gel permeation chromatography (GPC) performed on a Tosoh Ecosec HLC-8320GPC equipped with both refractive index (RI) and ultraviolet (UV) detectors (UV-detection, λ = 280 nm) using Tosoh alpha 2000 and 4000 and 2000 columns. DMF containing 10 mM LiBr was used as the solvent. Calibration curves were obtained using polystyrene standards. MALDI-TOF MS measurements were performed on a Bruker AutoFlexIII MALDI-TOF mass spectrometer. Perkin Elmer TGA7 thermogravimetric analyzer.
Bis-thyminyl monomers were synthesized using a previously reported method.\textsuperscript{15} The following is a typical procedure for the synthesis of bis-thyminyl monomers. Synthesis of dimethyl 3,3'-(3,3'-phenylenebis(methylene))bis(5-methyl-2,4-dioxo-3,4-dihydropyrimidine-3,1(2H)-dial) diopropanoate $\mathcal{S}$ : Thymine methyl propanoate (3.99 g, 14.8 mmol), K$_2$CO$_3$ (2.45 g, 17.8 mmol) and 1.4- bis(bromomethyl) benzene (1.56 g, 9.52 mmol) were combined in 50 mL MeCN under $N_2$. The mixture was refluxed for 20 h, cooled to ambient temperature and decanted into CH$_2$Cl$_2$ (150 mL). The salts were removed by filtration, and the solvent was evaporated from the filtrate to leave a solid which was twice triturated in EtOAc/EtOH (90:10).

**Dimethyl 3,3'-(3,3'-(butane-1,4-diyl)bis(5-methyl-2,4-dioxo-3,4-dihydropyrimidine-3,1(2H)-dial)) diopropanoate (1):** Yield: 75%. M.p.: 189.7-191.9°C. MS (ESI)$^+$: calcd for C$_{25}$H$_{23}$NO$_8$: m/z 479.2; found: m/z 479.1 (M+H)$^+$, 501.1 (M+Na)$^+$. 1H NMR (400 MHz, CDCl$_3$): $\delta$ 1.68 (m, 4H, 3-N$_3$-CH$_2$), 1.90 (d, $J = 1.2$ Hz, 6H, C$_5$-CH$_3$), 2.77 (t, $J = 6.4$ Hz, 4H, CH$_2$CO), 3.70 (s, 6H, OCH$_3$), 3.96 (t, $J = 6.4$ Hz, 8H, N$_3$-CH$_2$-N1-CH$_2$), 7.14 (d, $J = 1.2$ Hz 2H, C$_6$H$_3$). 13C NMR (100 MHz, CDCl$_3$): $\delta$ 12.9 (C$_5$-CH$_3$), 25.2 (N$_3$-CH$_2$), 32.9 (CH$_2$CO), 40.3 (N$_3$-CH$_2$), 45.7 (N1-CH$_2$), 51.9 (OCH$_3$), 109.4 (C5), 139.3 (C6), 151.2 (C2), 163.7 (C4), 171.9 (COOR). Selected IR bands (ATR, cm$^{-1}$): 3450 m, 2968 m, 2936 m, 1732 s, 1700 s, 1662 s, 1640 m, 1545 m, 1430 m, 1406 m, 1397 m, 1360 m, 1214 s, 1202 s.

**CHN analysis (calcld. found for C$_{25}$H$_{23}$NO$_8$: C (55.22, 55.35), H (6.32, 6.28), N (11.71, 11.64).**

**Dimethyl 3,3'-(3,3'-(propane-1,3-diyl)bis(5-methyl-2,4-dioxo-3,4-dihydropyrimidine-3,1(2H)-dial)) diopropanoate (6):** Yield: 80%. M.p.: 236.8-239.2°C. MS (ESI)$^+$: Calcd for C$_{23}$H$_{21}$NO$_7$: m/z 450.18; Found: m/z 473.0 (M+Na), 100%. 1H NMR (400 MHz, CD$_2$DMSO): $\delta$ 1.47 (br.s (t), 4H, core CH$_2$), 1.78 (s, 3H, C$_5$-CH$_3$), 2.61 (t, $J = 6.8$ Hz, 4H, CH$_2$CO), 3.78 (br.s (t), 4H, N$_3$-CH$_3$), 3.87 (t, $J = 6.8$ Hz, 4H, N$_3$-CH$_2$), 7.56 (s, 1H, C$_6$H). 13C NMR (100 MHz, CD$_2$DMSO): $\delta$ 12.54 (C$_5$-CH$_3$), 24.6 (N$_3$-CH$_2$), 32.7 (CH$_2$CO), 40.1 (N$_3$-CH$_2$), 45.0 (N1-CH$_2$), 107.3 (C5), 140.5 (C6), 150.6 (C2), 163.0 (C4), 172.2 (COOH). Selected IR bands (ATR, cm$^{-1}$): 3498 m, 3071 m, 2930 m, 2914 m, 1691 m, 1612 s, 1434 m, 1338 m, 1357 m, 1205 m. CHN analysis (calcld. found for C$_{23}$H$_{21}$NO$_7$: C (50.31, 50.59), H (6.12, 6.04), N (11.73, 11.83).**

**Dimethyl 3,3'-(3,3'-(butane-1,4-diyl)-bis(5-methyl-2,4-dioxo-3,4-dihydropyrimidine-3,1(2H)-dial)) diopropanoic acid (2):** Yield: 34%. M.p.: 111.9°C. MS (ESI)$^+$: Calcd for C$_{24}$H$_{22}$NO$_6$: m/z 492.2; Found: m/z 515.1 (M+Na)$^+$. 1H NMR (400 MHz, CD$_2$DMSO): $\delta$ 1.22 (p, $J = 7.4$ Hz, 4H, N$_3$-CH$_2$CH$_2$CH$_2$), 1.50 (p, $J = 7.4$ Hz, 4H, N$_3$-CH$_2$CH$_2$), 1.79 (d, $J = 0.8$ Hz, 6H, C$_5$-CH$_3$), 2.76 (t, $J = 6.0$ Hz, 4H, CH$_2$CO), 3.59 (s, 3H, OCH$_3$), 3.77 (t, $J = 7.2$ Hz, 4H, N$_3$-CH$_2$), 3.90 (t, $J = 6.0$ Hz, 4H, N$_3$-CH$_2$), 7.55 (d, $J = 1.2$ Hz 2H, C$_6$H$_3$). 13C NMR (100 MHz, CD$_2$DMSO): $\delta$ 13.0 (C$_5$-CH$_3$), 24.3 (N$_3$-CH$_2$CH$_2$CH$_2$), 27.3 (N$_3$-CH$_2$), 32.9 (CH$_2$CO), 41.2 (N$_3$-CH$_2$), 51.9 (OCH$_3$), 109.5 (C5), 139.4 (C6H), 151.2 (C2), 163.6 (C4), 171.8 (COOR). Selected IR bands (ATR, cm$^{-1}$): 3070 m, 2958 m, 1716 m, 1634 s, 1496 w, 1444 m, 1381 w, 1355 w, 1232 m, 1140 w, 1050 w, 938 w, 802 m, 766 w.
(CS), 139.2 (C6), 151.2 (C2), 163.7 (C4), 171.9 (COOR).
Selected IR bands (ATR, cm\(^{-1}\)): 3409 bw, 3085 w, 2954 m, 1732 m, 1696 m, 1662 s, 1637 s, 1509 m, 1460 m, 1429 m, 1381 m, 1355 m, 1203 s. CHN analysis (calcd, found for C\(_2\)H\(_8\)NO\(_3\)I): C 56.91, 57.01, H (6.77, 6.53), N (11.06, 10.92).

**Dimethyl 3,3′-O(1,4-phenylenebis(methylene))bis(5-methyl-2,4-dioxo-3,4-dihydroprindine-3,1(2H)-diyl)dipropionate (8):** Yield: 40%. M.p: 177.3-178.4°C. MS (ESI): Calcd for C\(_2\)H\(_8\)NO\(_3\): m/z 526.2. Found: m/z 549.0.

\(^{10}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.91 (s, 6H, C5-CH\(_2\)), 2.77 (t, J = 6.2 Hz, 4H, CH\(_2\)O), 3.69 (s, 6H, O-CH\(_3\)), 3.96 (t, J = 6.2 Hz, 4H, N-CH\(_2\)), 5.08 (s, 4H, N3-CH\(_2\)), 7.16 (s, 2H, C6H), 7.40 (s, 4H, Ar CH). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) C.13 (C5-CH\(_3\)), 13.2 (C3-CH\(_3\)), 60.6 (OCH\(_3\)), 110.8 (C1H), 128.6 (Ar CH), 135.8 (Ar C), 152.7 (C2, C4), 171.7 (COOH).

**Photo-product**: Yield: 40%. MS (ESI): m/z 547.8 (M+Na\(^{+}\)) (10%), 606.2 (2M+H\(^{+}\)) (3%), 655.2 (3M+Na\(^{+}\)) (9%). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) C.18 (C5-CH\(_3\)), 25.8 (C3-CH\(_3\)), 31.9 (C2H), 42.0 (C3H), 43.8 (CH3), 45.8 (CH3).

**Cryst. Data and Methods**: Crystal Data and Methods are included in the Supporting Information.

**General photo-product synthetic procedure**: A crystalline sample of the monomer was spread into a thin layer in a petri dish. The uncovered sample was irradiated with 302 nm for the time period specified in the relevant Results and Discussion sections (generally between 0.5 h-120 h). The crystalline material was agitated periodically during the irradiation to ensure that the crystals were evenly exposed to the UV light. Where appropriate, the photo-reactions were monitored by \(^{13}\)NMR spectroscopy and GPC.

**Photo-product 11**: Photochemical yield (\(^{13}\)NMR): 96%. GPC (DMF + 10 mM LiBr): \(M_N\) 19 x 10\(^{3}\) (\(D = 4.0\)).

**Photo-product 12**: Photochemical yield (\(^{13}\)NMR): 95%. MALDI-TOF (DCTB) showed photo-products up to m/z 9,495.

**Photo-product 13**: Photochemical yield (\(^{13}\)NMR): 81%. MALDI-TOF (sinapinic acid) showed oligomeric photo-products up to m/z 2,825.

**Photo-product 14**: Photochemical yield (\(^{13}\)NMR): 84%. GPC (DMF + 10 mM LiBr): \(M_N\) 2.2 x 10\(^{3}\) (\(D = 4.9\)).

The Cambridge Crystallographic Data Centre depositions: 841955, 841956, 841957, 888374, 948169, 948168, 948167 contain the supplementary crystallographic data for this paper. Detailed crystal structure information can also be found in the Supporting information.
(m, 2H, N1-CH2CH2), 2.76-2.84 (m, 2H, N1-CH2CH2), 3.24-3.31 (m, 2H, N1-CH2), 3.68 (s, 6H, OCH3), 3.82 (br. t, J = 7.4 Hz, 4H, N3-CH2), 3.92-4.05 (m, 2H, N1-CH2), 3.96 (s, 2H, C6H). 13C NMR (100 MHz, CDCl3): δc 19.0 (C5-CH3), 26.7 (N3-CH2CH2), 28.5 (N3-CH2CH2), 32.1 (C2-CH2), 33.1 (C5), 41.3 (N3-CH2), 43.9 (N1-CH2), 45.9 (N1-CH2), 52.2 (OCH3), 62.1 (C6), 151.5 (C2, C4), 172.1 (COOR). Selected IR (ATR, cm⁻¹): 2957 w, 1734 m, 1696 m, 1655 s, 1467 m, 1437 m, 1402 w, 925 w, 846 w, 753 m.

Photo-product 15. Photochemical yield (¹H NMR): 50%. GPC (DMF + 10 mM LiBr): Mn 1.0 x 10³ (D = 1.2). ¹H NMR (400 MHz, CDCl3): δH 1.42 (s, 6H, cyclobut. C5-CH3), 1.90 (s, 6H, thy. C5-CH3), 1.88-2.03 (m, 4H, N3-CH2CH2), 2.61-2.69 (m, 2H, cyclobut. CH2CO), 2.76-2.79 (m, 6H, 2 cyclobut. CH2CO + 4 thy. N1-CH2), 3.25-3.32 (m, 2H, N1-CH2), 3.65 (s, 6H, cyclobut. OCH3), 3.71 (s, 6H, thy. OCH3), 3.89-4.07 (m, 14H, 2 cyclobut. N1-CH2 + 4 N3-CH2, and 4 thy. N1-CH2 + 4 N3-CH2), 4.11 (s, 2H, cyclobut. C6H), 7.15 (s, 2H, thy. C6H). Selected IR (ATR2, cm⁻¹): 2951 w, 1734 m, 1696 m, 1655 s, 1467 m, 1437 m, 1402 m, 1372 m, 1346 m, 1284 w, 1202 m, 1147 m, 1042 m, 964 w, 925 w, 846 w, 753 m.

Results and discussion

Ten bis-thyminyl monomers were synthesized (1-10, Figure 2). Previous crystallographic and computational studies indicated that functionalization of the N1 nitrogen of thymine with methyl propanoate successfully eliminated other disruptive interactions, and facilitated desirable π-π stacking of thyminyl rings in the crystal. As such, many of the synthesized bis-thyminyl monomers possess N1 methyl propanoate functionality (1, 5-10), although an acetate derivative (4) was also examined for comparative purposes. It was also expected that the size of N3-N3 spacer groups would affect the crystal packing environment of the monomers, and that the properties of the photo-products would be influenced by type of N3-N3 spacer used (flexible or rigid). Therefore, in order to systematically investigate the crystal packing behaviour and the photo-chemical reactions of crystalline bis-thyminyl monomers, ten novel monomers were synthesized, varying with respect to the N1-functionality (Figure 2, a), the size of the N3-N3-polyethylene spacer (b), or the type of rigid N3-N3-aryl spacer (c).

Bis-thyminyl monomers were synthesized as follows (Scheme 1). Thymine methyl propanoate was synthesized by Michael addition of methyl acrylate to thymine. The corresponding amide derivatives were subsequently formed by the aminolysis of thymine methyl propanoate. Thymine methyl acetate was synthesized by acid catalyzed esterification of thymine acetic acid. In most cases, the synthesized N1-derivatives were linked by N3 bridging using a relevant dibromo- or diiodo-bridging compound. The dipropanoic acid monomer 2, was an exception in that it was synthesized by base hydrolysis of the dipropano ester monomer (1) in order to avoid a possible side reaction between 1,4-dibromobutane and the free carboxylic groups.

Synthesized bis-thyminyl monomer crystals (10-50 mg) were irradiated with 302 nm UV light for a period of 17 h, and the irradiated samples were subjected to ¹H NMR analysis to determine the photo-reactivity of each crystalline sample. Referring to Table 1, a total of 5 monomers (1, 2, 5, 7, 8) were photo-reactive.

In order to examine the changes to crystal packing brought about by the chemical structure of the bis-thyminyl monomers and to also identify suitable topochemical arrangements for solid crystalline photo-chemical reactions, the crystalline monomer samples were subjected to structural analysis using X-ray diffraction. Where possible, the crystal structures of monomers were obtained by single crystal-XRD performed at the Australian Synchrotron using the microcrystallography beamlines. Table 1 summarizes some key structural information obtained from the analyses (complete crystal structure information can be found in the Supporting Information). In some instances (4, 6 and 8), suitable quality single crystals were not obtained and powder-XRD was instead used to fingerprint the crystalline samples (data can be found in the Supporting Information). As can be seen from the results in Table 1, the cis-syn thymine ring-pairing in amide 3 was unique amongst the monomers investigated, and this orientation was stabilized by extensive hydrogen bonding at the amide moieties. The other monomer structures obtained, all demonstrated trans-anti type packing arrangements with respect to the proximity-related thyminyl units. This demonstrates, to some degree, that the propanoate moiety preferentially adopts trans-anti type arrangements in the lattice.

In the cases where trans-anti type ring pairs were observed, we noted that the proximity-related thyminyl ring pairs in the monomer crystals packed in three different ways, Type I, Type II, and Type III (Figure 3). Type I and II packing both involved bent propanoate chain conformations, but in one case the propanoate chains bent inward toward the thyminyl ring stack (Type II); while in the second, the propanoate chains bent away from the thyminyl ring stacks (Type I).

As it is known that olefin pairs only react when they align parallel with one another in the lattice, and are separated by a distance of 3.5-4.2 Å,19 the distance between closest thymine pairs is an important parameter for predicting the relationship between photo-reactivity and the crystal structure of the monomers.

Type I stacking was observed in the (photo-active) proximity-related thyminyl pairs of the propanoate (1) and propionic (2) monomer structures. In these cases, the olefinic separation distance between the proximity related thyminyl rings were close (ca. 4.2 Å), and within the reported range for photodimerization.20 Type II stacking appeared to be stabilized by weak C=C=C=O(ester) interactions in the structures of the n-hexyl (7) and n-propyl-linked (5) monomers, but the motif was displaced in the dimethoxyaryl (9) and diethoxyaryl-linked (10) monomer structures. The Type II stacking of proximity-related
Table 1. Summary of the photo-activity and crystal structure data obtained for the bis-thyminyl monomers.

<table>
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<tr>
<th>Monomer</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>0</td>
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<td>-</td>
<td>Row</td>
<td>-</td>
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<tr>
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<td>Bent</td>
<td>Linear</td>
<td>-</td>
<td>Bent</td>
<td>-</td>
<td>Bent</td>
<td>-</td>
<td>Bent</td>
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</tr>
<tr>
<td>N3 conf.</td>
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<td>trans</td>
<td>-</td>
<td>cis</td>
<td>-</td>
<td>trans</td>
<td>-</td>
<td>trans</td>
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<tr>
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<td>TA</td>
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<tr>
<td>Packing of closest thymine pair</td>
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<td>Type I</td>
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<td>Type II</td>
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<td>4.67</td>
<td>-</td>
<td>4.97</td>
<td>4.67</td>
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</table>

a Proximity-related thyminyl pairs form trans-anti (TA) or cis-syn (CS) type arrangements; not applicable (n/a)

Figure 3. Three observed trans-anti ring stacking motifs in crystal structures of bis-thyminyl monomers.

thyminyl pairs in the structures of 5, 7, 9 and 10 was accompanied by larger olefinic separation distances (4.68, 4.67, 4.97 and 4.67 Å, respectively) which was over the reported range for photo-dimerization. The distance between the proximity related thyminyl rings in Type III was close (ca. 3.78 Å) and within the reported range for photo-dimerization.

The photo-reactivity of 1 and 2 with Type I stacking and 5 with Type III stacking can be explained by the distance between the proximity related thyminyl rings, however, the photo-reactivity of 7 which has Type II stacking can not be explained by the distance between rings.

The photo-reactivity of 7 with Type II stacking could be explained by the increase of attractive forces at electronic excitation. It is known that excited-species can interact more strongly with neighbouring molecules in the lattice. In situations where the double bonds are not stacked parallel in the lattice such attractive forces could bring the olefin of an excited state species into close enough proximity with a ground state olefin to enable interaction of the π-lobes and hence facilitate [2π+2π]-cycloaddition. In fact, supportive evidence is presented in a published theoretical study which indicates that, in DNA, the geometry of the excited thyminyl species undergoes pyramidalization of the C6 atom and C5-C6 bond lengthening in order to give the cis-syn cyclobutane dimer via a concerted mechanism. In the case of the photo-stable aryl linked monomers (9 and 10), the arrangement of the olefins is more relevant. Referring to the schematic in Figure 4, the thyminyl ring stacking of 9 and 10 is laterally and vertically displaced compared to 7. As such, C5-C6 bond lengthening and C6 pyramidalization are unlikely to facilitate π-π interactions in this case, and therefore these crystals remain photo-stable.

Despite not having a crystal structure for 4, the photo-stability of 4 can be explained based on the crystal structure of the starting material, methyl acetate. In the crystal structure of the starting acetate, an intermolecular carboxyl-carbonyl C=O-O=O (d = 2.96 Å, C2=O = 108˚), and an intermolecular C=O interaction (d = 2.61 Å, C=O-H = 143˚) were observed. As occurred in the starting acetate crystal structure, these weak interactions are expected to effectively compete with the π-π stacking interactions in crystal structure of 4, thereby disrupting the ideal ring packing required for photo-dimerisation.

It is interesting to note that 6 was photo-stable even with a very similar structure to 1, 5, and 7. The only difference between these monomers is the length of N3-N3 n-alkyl spacer. According to the crystal structures, the monomers with even spacers (C4 and C6/I and 7) caused up-down orientation of the thyminyl propanoate moieties within the monomer molecule, while the odd C3 spacer (5) caused both propanoate groups to point in the same direction. In the case of monomers with an even spacer, the monomer molecules packed in the same direction as another. Conversely the C3 (5) structure showed that the molecular orientation of the monomers alternated, and were related to one another by a 180˚ rotation. As a consequence, the stacking of the thyminyl rings of the monomers became different for the odd and even spacers and this could be the reason for the photo-stability.
of 6. Unfortunately, more compounds and crystal structures are required in order to make firm conclusions concerning the effects of spacer length on the photo-reactivity of the monomers.

Identification of the photo-products
Considering the continuous and juxtaposed alignment of monomer molecules in the crystal structures as well as the high photo-chemical yields determined from the $^1$H NMR spectra of the photo-products of 1, 2, 5, 7 and 8 (Table 1), it was expected that linear polymeric species would arise from the irradiation of these monomer crystals (Scheme 2). As such, techniques including GPC, MALDI-TOF MS and $^1$H NMR spectroscopy were used to determine the molecular weights of the photo-products. The measured molecular weights from these techniques are shown in Table 2. Unreacted monomers were able to be separated from the polymers by precipitation of the polymers.

![Scheme 2. Synthesis of photo-products](image)

Photo-products obtained from the irradiation of 1, 5, and 7 were soluble in CDCl$_3$, DMF and DMSO; while the photo-products of 2 were soluble in DMF, DMSO and alkaline water. The photo-products of aryl-linked 8 were found to be insoluble in common organic solvents, and only trifluoroacetic acid (TFA) and TFA/CHCl$_3$ (25:75) were found to solubilize the photo-products. This feature certainly suggested a qualitative difference in the properties of the photo-products of the alkyl- and aryl-bridged compounds.

Table 2 Summary of the molecular weights determined for irradiated samples of monomers

<table>
<thead>
<tr>
<th>No.</th>
<th>GPC $M_n$ (x 10$^5$)</th>
<th>MALDI-TOF MS$^a$</th>
<th>$^1$H NMR $m/z$</th>
<th>MALDI-TOF MS$^a$</th>
<th>$^1$H NMR $M_n$ (x 10$^5$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>9,611</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>2,825</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>1.2</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>4.9</td>
<td>-</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>9,495</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Highest detected $m/z$ in the MALDI-TOF mass spectrum.

Although the photo-products of 2 were soluble in the DMF mobile phase used for GPC, the analysis was unsuccessful due to the interaction of the monomer and photo-products with the GPC column, which resulted in a poor elution profile. Even when the LiBr content of the DMF was increased to 50 mM, or the material was analyzed from an aqueous mobile phase, reliable chromatograms could not be obtained. Furthermore, the purified photo-products of 8 could not be analyzed by GPC as they were insoluble in all the common organic solvents as mentioned previously.

Therefore, MALDI-TOF MS, was utilized to study the molecular weight of polymeric products derived from monomers 1, 2 and 8. Analyte ions were observed using the 2-(2E)-3-(4-tert-butylphenyl)-2-methylprop-2-ynlidene]malononitrile (DCTB) matrix with the polymeric products derived from 1 and 8, and when an sinapinic acid (SA) matrix, was used with the photo-products derived from 2. Figure 5 shows the MALDI-TOF mass spectra obtained from these analyses. The main ion peaks in each spectrum are separated (on average) by $m/z$ values corresponding to the monoisotopic molecular weight of the repeating monomer unit (M) or M+1, which confirms that the ions originate from the analyte samples.

![Figure 5. MALDI-TOF Mass spectra obtained for the photo-products. (a) Photo-products of 1 (b) photo-products of 8 (c) photo-products of 2](image)

The analyte sample used to obtain the spectrum in Figure 5 (a) was the polymeric photo-product of 1 which, from GPC analysis, possessed an $M_n$ of 1.9 x 10$^5$ (Table 2). In the corresponding MALDI-TOF mass spectrum, however, the result is clearly skewed to lower $m/z$ values and for this reason only the largest analyte ion ($m/z$ 9,611) is quoted in Table 2. Similarly skewed mass spectra were obtained using the photo-products of 8 and the oligomeric products prepared 2.
The structure of the obtained photo-products was further identified by $^1$H NMR and IR and the disappearance of the olefin and the formalisation of cyclobutane ring were confirmed in every product. The photo-product from 5 was identified as a dimer molecule from $^1$H NMR. Unfortunately, crystal structures of the photo-products could not obtained by single crystal-XRD due to the irradiation-induced fracture of the crystals. Accordingly, powder X-ray diffraction spectra of all photo-products were analyzed. In summary, the irradiation of five different crystalline photo-active monomer samples generated several new products, as shown in Figure 6. Monomers 1 and 8 formed polymers 12 and 13, respectively. Both 2 and 7 gave oligomeric photo-products 13 and 14, respectively, while monomer 5 produced linear dimeric molecules 15 upon irradiation.

Figure 6. Identified photo-products obtained from the irradiation of crystalline monomer samples. $n > 35$, $m < 10$.

The $^1$H NMR spectra obtained for the irradiated monomer samples were used to determine the percentage conversion of two thyminyl units to one cyclobutane unit, by comparing the integration values of (non-reacted) thyminyl C5-CH$_2$ and methyl protons and (reacted) cyclobutane C5-CH$_2$ and methyl protons. Figure 7 reveals the calculated percentage conversion to cyclobutane for the photo-chemical reactions. Collectively, these results indicate that most of the conversion to cyclobutane occurs during the first 10 h irradiation. In the first 10 h, both the butyl-linked bis-propanoic acid (2→13) and aryl-linked bis-propanoate (8→12) systems underwent the greatest amounts of conversion to cyclobutane (80 and 81%, respectively). The butyl-linked bis-

propanoate sample, 1→11, exhibited slightly lower reactivity during the first 10 h period as it underwent 70% cyclobutane conversion. Beyond 10 h irradiation, however, additional conversion to cyclobutane occurred more gradually in all the samples.

Figure 7. $^1$H-NMR Conversion of thyminyl methyl moieties to cyclobutane methyl moieties over a 57 h irradiation period

**Thermal Properties of polymers**

Thermal properties of the prepared thyminyl cyclobutane polymers were studied using a combination of TGA and DSC. The TGA thermograms obtained for each material are shown in Figure 8.

Figure 8. TGA Thermograms of polymers

For all the thyminyl materials tested, the largest percentage of mass loss was observed during the second mass loss stage which occurred between 329-470°C. The degree of mass loss observed in the second stage (52-62%) could not be attributed to the degradation or loss of any single structural component of the materials. Considering the similar sublimation temperatures reported for other thyminyl compounds (eg. 378-428°C for thymine, 373-423°C for N1-methyl thymine, and 313-363°C for N1,N3-dimethyl thymine$^{31}$), it is proposed that the second mass loss stage in the thermograms of the thyminyl materials arises due to sublimation of the degradation products. Moreover, in the second mass loss stage, the maximum rates of mass loss were...
observed over a narrow 12°C temperature range ($T_{\text{max}}$ 393-405°C) which could indicate the sublimation of closely related decomposition products in all of the samples. The temperature corresponding to 10% mass loss ($T_{\text{10\%}}$) was found to range between 269-311°C in the materials. Oligomeric 14 resulted in the lowest measured 10% degradation temperature of $T_{\text{10\%}}$ 269°C.

DSC analyses were performed in order to study the thermal transitions of the materials, such as possible glass transition temperatures ($T_g$) and polymer melting temperatures ($T_m$) (Figure 9). The DSC curve for 14 showed an endothermic deviation at 132°C. As monomer 7 has a melting point of 140°C, which is very close to the endothermic peaks observed in the DSC curve, it is proposed that this peak could be from residual monomer present in the sample (as conversion of this polymerization was only calculated from NMR to be ca. 80%, Figure 7).

![Figure 9. DSC curves of polymers](image)

Figure 9. DSC curves of polymers

A step transition of small magnitude (60 mW.g$^{-1}$) was detected in the DSC curve of 12 at 94°C which potentially represents the glass transition temperature ($T_g$) (Figure 9, inset). As proven by the P-XRD spectrum of 12, the material is highly crystalline. This would account for the low magnitude glass transition observed by DSC.5

The most obvious features of the DSC traces for 11 are the series of endothermic deviations. A number of unusual endothermic peaks were observed at 148°C, 167°C and 213°C in the DSC trace. An apparent step transition was also observed at 74°C in the DSC curve, although it was of low magnitude (35 mW.g$^{-1}$). A subsequent measurement by DMTA provided an approximate value of $T_g = 77^\circ$C,5 which supported the classification of the small endothermic DSC step at 74°C, as the glass transition. To determine the precise origin of the endothermic peaks occurring between 148-213°C in the DSC curve of 11, polarised optical microscopy was used to examine the textural changes in 11 during heating, and GPC and $^1$H NMR analyses were performed on samples of 11 after they were heated in the DSC apparatus. As a result of these experiments, the peak at 213°C was attributed to the melting peak of polymer 11, while the other peaks were attributed to decomposition (depolymerization) events.

Indeed the $^1$H NMR spectra of 11 heated to 140±3°C for various periods of time - either in DMF solution, or as solids with and without N$_2$ flow revealed signs of depolymerization. After 24 h at 140±3°C, $^1$H-NMR spectra of the thermally treated materials showed prominent peaks at δ 7.15 ppm and δ 1.90 ppm, which corresponded with the olefinic C6H and C5-CH$_3$ protons of the monomer, respectively. This in turn indicated that the thermal treatment caused depolymerization which resulted in an increase to the relative content of monomer molecules or terminal thyminyl groups present. The ratio of cyclobutane C5-CH$_3$ protons (δ 1.37 ppm) to thyminyl C5-CH$_3$ protons (δ 1.90 ppm) changed from 98% to 80% as a result of the thermal treatment. In addition to depolymerization, the $^1$H-NMR spectra of the treated samples also displayed new peaks in the downfield regions between δ 8.17-9.82 ppm. The appearance of new peaks above δ 8.0 ppm could indicate some degree of thermal decomposition to give NH or COOH moieties, or the new peaks could merely be the result of different proton environments present in the oligomeric depolymerization products. The thermally-induced depolymerization of 11 was also measured by GPC at various points throughout a 24 h heating period (Figure 10), it was apparent that depolymerization occurred rapidly at 140°C. After just 10 min, the average molecular weight of the starting polymer decreased by 67% in open-air conditions, 73% when heated under a N$_2$ stream, and 85% when heated in DMF. Depolymerization continued rapidly over the first hour, but slowed beyond that time. The GPC result showed that after 24 h the average molecular weight had decreased from $M_n$ 6.3 x 10$^5$, to 3.6 x 10$^5$ and 3.3 x 10$^5$ for the solids heated with and without N$_2$ (respectively), and 1.3 x 10$^5$ for the solution-phase depolymerization.

![Figure 10. Changes to the average molecular weight of polymer 11](image)

Figure 10. Changes to the average molecular weight of polymer 11 samples that were heated at 140°C for various time periods in either DMF solution (solid triangle), or as solids in the presence (open circle) or absence (closed circle) of N$_2$ flow.

Interestingly, when the thermal stability of the aryl-linked polymer 8 was studied over a similar range of temperatures, the $^1$H NMR spectra of the thermally treated polymer samples showed no significant change in the integration ratio of the thyminyl C5-CH$_3$ and cyclobutane C5-CH$_3$ protons. Therefore, it appeared that 8 did not undergo depolymerization over the temperature range of 20-140°C, and in this way aryl-linked material (8) appeared to be more thermally stable than the butyl-linked material (11). The improved thermal stability of the aryl-
linked polymer (12) showed potential for tuning the properties (eg. thermal stability, processibility, and photo-sensitivity) of the resulting polymers by modulating the monomer-polymer system design.

Conclusions

Ten thyminyl monomers were synthesized, that varied with respect to the N1-functionality, the size of the N3-N3-polymethylene spacer, or the type of rigid N3-N3-aryl spacer. On irradiation, five of the crystalline monomers were found to undergo topochemical photo-reactions. The n-propyl linked monomer (5) produced open dimeric molecules (15) upon irradiation, while both the n-hexyl-linked bis-methyl propanoate (7) and n-butyl-linked bis-propanoic acid (2) monomers gave oligomeric photo-products (14 M<sub>n</sub> 2.2 x 10<sup>3</sup>, D = 4.9; 13 m/z 2,825, respectively). The n-butyl-linked bis-methyl propanoate (1) gave polymeric photo-products (11) with variable molecular weights (typically M<sub>n</sub> 1.9 x 10<sup>4</sup> and higher). The aryl-linked monomer (8) also produced polymeric photo-products (12) upon irradiation (ca. M<sub>n</sub> 1.1 x 10<sup>3</sup>).

From the thermal properties measurements, thermally-induced depolymerization of polymer 11 was observed. The aryl-linked polymer (12), however, did not appear to undergo thermal depolymerization and this indicated that the properties of polymers can be controlled by the structure of monomers for the solid-crystalline photo-polymerization.

Acknowledgement

We thank Dr Craig Forsyth, Dr David Turner, and the Australian Synchrotron MX beamline staff for any help they have provided with the crystallographic experiments; Prof. Roy Jackson, Ass. Prof. Tony Patti, Prof. George Simon and Dr. John C. Warner for many fruitful discussions. We also acknowledge the financial support of the Monash University Faculty of Science Early Career Research Fund

Notes and references

Bis-thyminyl monomers were found to undergo topochemical photo-reactions and form polymers by $[2\pi + 2\pi]$-cycloaddition.