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Synthesis of a hydrophilic phosphonic acid monomer for dental materials

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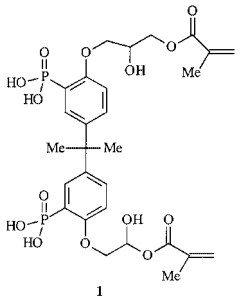
A novel phosphonic acid monomer for use in dental composites was prepared by the base-catalysed rearrangement of the corresponding diethyl arylphosphonate.

In general dentistry may be described as a profession that is engaged with the repair and treatment of the teeth in order to restore proper function and good aesthetics. One of the major problems encountered in the treatment of teeth is dental caries, which is a preventable condition but one that is widespread and is possibly the most common disease in the world.[1] The onset of dental caries is due to metabolic activity by the bacteria of the plaque leading to production of acids from sugar in the diet, resulting in a localised attack on the enamel and dentine of the tooth.[2] The infection caused by caries can lead to other more serious conditions and can be fatal in the case of endocarditis,[3] and as a consequence dental repair can be seen as important. Repair materials have been the subject of considerable research, with recent emphasis on aesthetic materials that are capable of bonding to the cleaned tooth surface.

In the present work, we have sought to prepare an acid-functional monomer for use in dental restorative materials. There are existing filling materials that contain acid-functional monomers, but they are aliphatic, and the resulting materials have relatively poor mechanical properties.[4] We anticipate that aromatic monomers, such as **1**, will yield materials with



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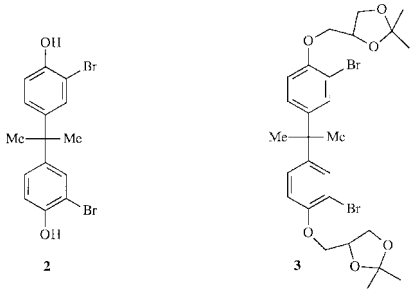
improved mechanical properties, because of the similarity with the aromatic dimethacrylate monomers currently used extensively in dentistry.

We also reasoned that the incorporation of a phosphonic function into monomer structures would result in increased biocompatability and adhesion to the tooth due to chelation with calcium ions in the tooth surface.

Here we report on the synthesis of the novel monomer **1** in which we have incorporated a phosphonic acid residue in both aromatic rings as well as incorporating a methylmethacrylate function that is capable of ionic or radical polymerisation.

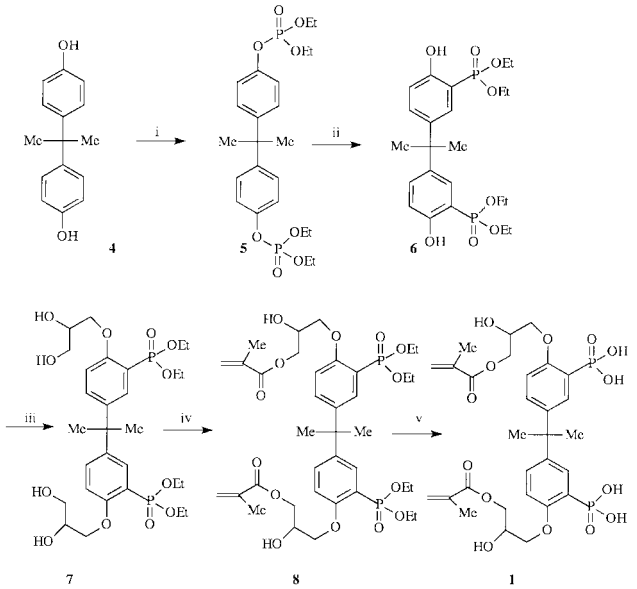
At the outset we investigated the formation of the aryl phosphonate **6** employing Michaelis–Arbuzov reaction with the 2,2′-dibromobisphenol **2** and triethyl phosphite and with *O*-dimethoxy analogues under a wide range of conditions,[5] and all of these attempts proved to be unfruitful. As a result of these findings we explored the chemistry of the di-*O*-isopropylidene protected dibromoaryl ether **3** employing Michaelis–Arbuzov conditions and also the Hirao modification.[6] Once again these attempts at the introduction of the phosphonate group proved to



2 **3**

be unfruitful. The alternative strategy of lithio anion formation.[7] followed by subsequent trapping led to complex mixtures that contained a small amount of the desired product, as evidenced by NMR.

Our successful approach to the synthesis of **1** is detailed in reaction Scheme 1. Bisphenol **4** was treated with NaH and chlorodiethylphosphite and afforded the di-*O*-phosphate **5** in 50% yield.† An improved yield (75%) of **5** was obtained if the reaction was conducted using diethyl phosphite in the presence of CCl_4 and triethylamine.[8] With the diphosphate **5** in hand we examined its rearrangement to the C-phosphonate as similar processes had been reported by Melvin at Pfizer[9] for simpler systems.[10] Thus treatment of the diaryl phosphate **5** with a 2.5 fold excess of lithium diisopropylamide at −78 °C resulted in the clean rearrangement to the diarylphosphonate **6** in 86% isolated yield after recrystallisation. That the rearrangement had occurred to give **6** was strongly supported by its spectral properties, in particular the ^1H, ^{13}C and ^{31}P NMR were most



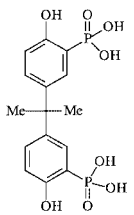
Scheme 1 *Reagents and conditions*: i, NEt_3 (2 equiv.), diethyl phosphite (2 equiv.), CCl_4, room temp., 30 h; ii, LDA (5 equiv.), THF, −78 °C, 1 h, then 3 h at room temp.; iii, glycidol (5 equiv.), cat. NEt_3, heat, 3 h; iv, Py, methacrylic anhydride (3.5 equiv.), cat. DMAP, room temp., 18 h; v, TMSBr (9 equiv.), room temp., 18 h, followed by aq. MeOH.

informative. In the ^{1}H NMR there was significant ^{1}H–^{31}P coupling to the *ortho* and *meta* protons (J_{P-H} 11.2 and 7.2 Hz) of the aromatic rings; this coupling was absent in **5**. In the ^{13}C NMR, coupling of ^{13}C–^{31}P was observed for the aromatic resonances (J_{C-P} 179.6, 13.5 Hz). The ^{31}P NMR also provided convincing support for the assignment, as the resonance due to the phosphonate was observed at δ −21.54 for **6** whilst in the phosphate **5** the resonance was found to be at δ −7.21.

This type of rearrangement reaction most likely proceeds *via ortho*-directed metallation of the aromatic ring followed by migration of the phosphorus to the cabanion centre, resulting in the formation of the phenolic phosphate. During the course of these studies we examined this rearrangement using ^{31}P NMR but we were unable to detect any intermediates during this process. We believe that this is the first example of this type of double phosphate rearrangement to provide the diphosphonate **6**.

Having the desired arylphosphonate **6** in hand alkylation of both the phenolic functions was accomplished with glycidol in the presence of triethylamine to afford **7** in 50% yield. Selective methacrylation of the primary hydroxy functions at both termini was accomplished with either methacroyl chloride in the presence of pyridine or with methacrylic anhydride in the presence of a catalytic amount of DMAP. The latter sequence was preferred as it gave rise to the desired product **8** in 50% yield as compared to 29% for the former reaction procedure. In both of these esterification reactions we observed the formation of doubly and singly esterifed products that were separated by column chromatography. The mono ester thus obtained could be converted to the diester on further treatment with either of the two acylating agents.

At this juncture it remained for us to selectively remove the ethyl ester protecting group of the phosphinates in **8**. We examined a range of procedures, including acid and base hydrolysis, and all of these methods proved to be unfruitful, with many resulting in C–O bond cleavage and removal of the methacroyl group. As a result of this we undertook model deprotection experiments with both the phosphonates **5** and **7** using trimethylsilyl bromide.[11] This treatment resulted in the formation of the respective phosphonic acids **9** and **10** as



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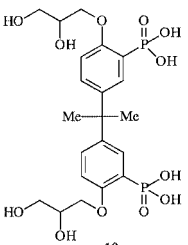

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dicyclohexylammonium salts, after hydrolysis, in yields of 55 and 96%. As a result of these findings we used trimethylsilyl bromide followed by hydrolysis with aqueous methanol to undertake the removal of the phosphonate ester groups and gratifyingly this afforded the desired acid monomer **1** in 60%. Alternatively, it could be isolated as its dicyclohexylammonium salt.

In summary, we have successfully developed the synthesis of the phosphonic acids **1** employing a double phosphate rearrangement reaction in excellent overall yield.

Polymerisation studies of **1** will be reported elsewhere. To date preliminary biocompatability studies are showing promise and these are ongoing.

We thank the EPSRC for support of this work and for access to central facilities for high resolution mass spectrometric data at the University of Wales, Swansea.

Notes and references

† All new compounds gave satisfactory spectral, microanalytical and/or high resolution mass spectrometry. *Selected data* for **1**: δ_H(270 MHz, $CDCl_3$) 1.65 (s, 6H), 1.95 (s, 6H), 3.76–4.29 (m, 12H), 5.66 (m, 2H), 6.18 (s, 2H), 6.85 (br d, 2H, *J* 5.1), 7.28 (br d, 2H, *J* 8.5), 7.84 (br d, 2H, *J* 14.1); δ_P(109.25 MHz, $CDCl_3$) +18.48; δ_C(67.8 MHz, $CDCl_3$) 30.55, 41.83, 41.85, 64.62, 67.87, 70.92, 112.92 (J_{C-P} 10.9), 117.04 (J_{C-P} 189), 125.93, 131.62 (J_{C-P} 13.5), 132.35 (J_{C-P} 4.5), 135.84, 143.11 (J_{C-P} 21), 158.39 (J_{C-P} 3.6 Hz), 167.04; ν_{max}(thin film)/cm^{-1} 3324–2716, 1720, 1600, 1490, 1294, 1168, 941 (found: M^+ + H, 673.1840, $C_{29}H_{39}O_{14}P_2$ requires 673.1815; dicyclohexylammonium salt (FAB) found: M^+ + H, 1035, $C_{53}H_{85}N_2O_{14}P_2$ requires 1035). For **5**: δ_H(270 MHz, $CDCl_3$) 1.28 (t, 12H, *J* 7.2), 1.62 (s, 6H), 4.12 (q, 8H, *J* 7.2), 7.03–7.33 (m, 8H); δ_P(109.25 MHz, $CDCl_3$) −7.21; δ_C 15.98 (d, J_{C-P} 6.7), 30.81, 42.17, 64.43 (J_{C-P} 6.0), 119.31 (J_{C-P} 4.9), 127.96, 146.98 (J_{C-P} 1.3), 148.63 (J_{C-P} 7.1); ν_{max}(thin film)/cm^{-1} 3451, 3281, 1604, 1505, 1271, 1033, 967. For **6**: mp 93–94 °C; δ_H(270 MHz, $CDCl_3$) 1.28 (t, 12H, *J* 7.2), 1.62 (s, 6H), 4.10 (q, 8H, *J* 7.2), 6.86 (dd, 2H, *J* 9.5, 7.2), 7.20 (dd, 2H, *J* 11.2, 2.6), 7.23 (dd, 2H, *J* 9.5, 2.6); δ_P(109.25 MHz, $CDCl_3$) −21.54; δ_C(67.8 MHz, $CDCl_3$) 16.09 (d, J_{C-P} 6.2), 30.67, 41.65, 64.64 (J_{C-P} 4.7), 108.04 (J_{C-P} 179.6), 117.38 (J_{C-P} 13), 128.80 (J_{C-P} 7), 134.06 (J_{C-P} 2.1), 141.42 (J_{C-p} 12.7), 160.17 (J_{C-P} 7.2); ν_{max}(KBr)/cm^{-1} 3451, 3137, 1602, 1405, 1209, 1027, 979.

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