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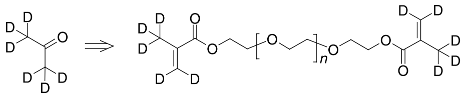
Graphical Abstract



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Partial Deuterium Labeling of Dimethacrylate Monomers

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Summary. Methacrylic acid-d_5 was prepared in a yield of 30% with 98.6% deuterium incorporation using a two step synthesis. A solution of acetone-d_6 and KCN in D_2O was treated with glacial acetic acid to give the cyanohydrin of acetone-d_6. The latter compound was then dehydrated in anhydrous sulfuric acid at 120°C and subsequently hydrolysed in water at 90°C to form methacrylic acid-d_5. Hydrolysis of commercial nonaethyleneglycol dimethacrylate gave a mixture of ethylene glycols. These glycols were combined with methacrylic acid-d_5 in the presence of *p*-*Ts*OH in benzene to form nonaethyleneglycol dimethacrylate-d_{10} with ~21% deuterium incorporation. Deuterated *bisGMA* was also prepared from methacrylic acid-d_5 and diglycidyl ether of bisphenol-A.

Keywords. Methacrylic acid-d_5; SANS; Nonaethylene glycol dimethacrylate; *bisGMA*-nonaethyleneglycol dimethacrylate-d_{10}; *bisGMA*-d_{10}.

Introduction

Dimethacrylate monomers are used in a range of applications including dental materials [1] and ophthalmic lenses [2], and are often involved in the blending of two or more monomers, making analysis of the cured structure difficult. In some cases, these mixtures of monomers may even phase-separate, which can have significant effects on their properties [3]. Whether phase separation has occurred and to what degree can be determined by small angle neutron scattering (SANS), if one of the components is deuterated [4]. Such measurements use differential scattering of the neutrons from the two phases to distinguish a single phase from a two phase structure. In this work, we developed a simple method of synthesizing deuterated methacrylic acid and partially deuterium labeled two methacrylate monomers.

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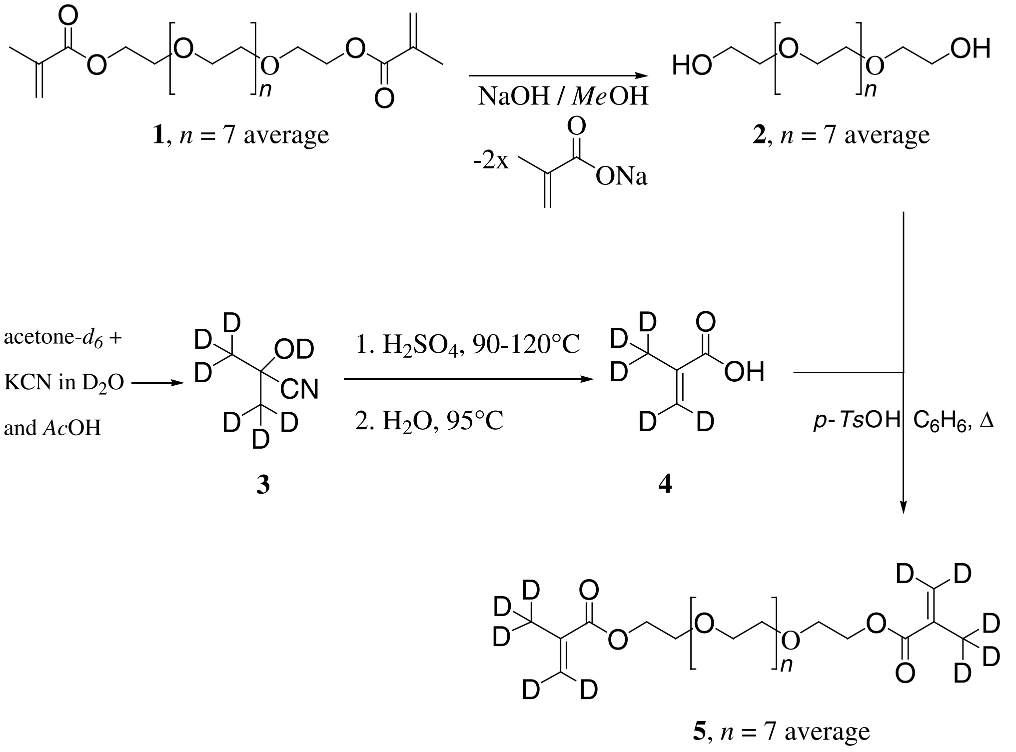
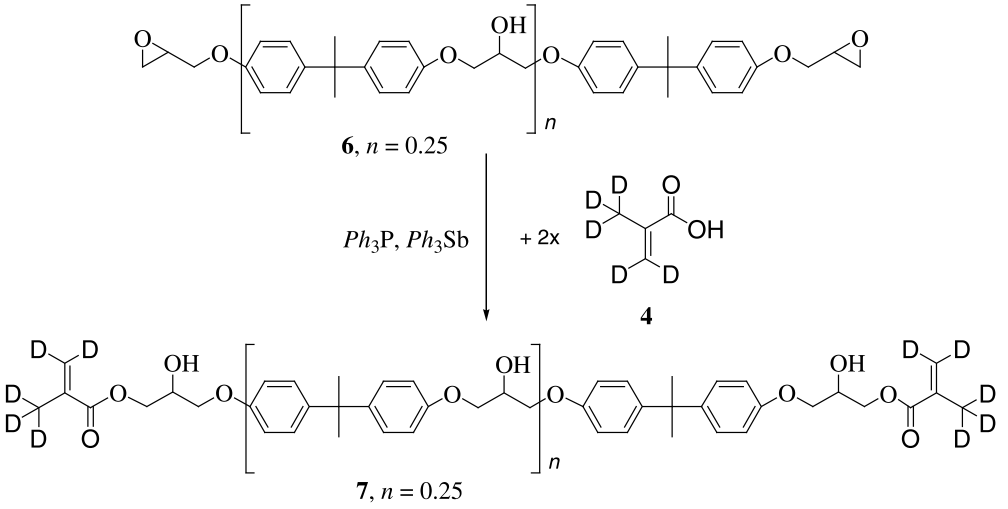


Scheme 1

One of the monomers investigated in this study was the flexible nonaethyleneglycol dimethacrylate (**1**) (Scheme 1). The length of the spacer group of the commercially available monomer actually varies and contains dimethacrylates where the ethylene glycol units contain not only 9 but a range from >7 to <12 ethylene glycol units [5]. Therefore, our approach was to first hydrolyse **1** to obtain



Scheme 2

the mixture of oligoethylene glycols (**2**), then reassemble (**1**) with methacrylic acid-d_5 (**4**) to provide fully deuterated methacrylate units (**5**) (Scheme 1). Another common monomer used in dentistry and lens manufacture is the very rigid monomer, bisphenol-A diglycidyl ether dimethacrylate, commonly known as *bisGMA*. A deuterated form (**7**) of this was prepared from bisphenol-A diglycidyl ether (**6**) and methacrylic acid-d_5 (**4**) (Scheme 2).

Results and Discussion

Methacrylic acid-d_5 (**4**) is commercially available, but costly. Literature does reveal some synthesis routes to obtain **4**. The Pd-catalysed deuterium exchange of methacrylic acid in D_2O at 100°C has been unsuitable to be carried out in the laboratory [6–8]. However, acetone-d_6 is relatively inexpensive and readily available. Thus, our approach for the preparation of methacrylic acid-d_5 (**4**) was taken from the work of Wako Ltd [9] which is based on the known synthesis for methacrylic acid, namely the dehydration and hydrolysis of the cyanohydrin of acetone [10] as shown in Scheme 1. Preparation of the cyanohydrin **3** was thus easily accomplished in a yield of 90% by addition of glacial acetic acid to a solution of acetone-d_6 and KCN in D_2O. This synthesis is a better method, producing higher yields than found in some literature procedures; for example, using concentrated H_2SO_4 [11, 12], D_2SO_4 [13, 14], Me_3SiCN/ZnI_2 [15], or Me_3SiCN/ZnI_2 [16]. Transformation of acetone-d_6 cyanohydrin (**3**) was successfully carried out in anhydrous sulfuric acid at 90–120°C, followed by the hydrolysis in D_2O of the intermediate amide to give the desired methacrylic acid-d_5 (**4**) in a modest yield of 30% after repeated purification with >98.6% deuterium incorporation [17–19].

Hydrolysis of nonaethyleneglycol dimethacrylate (**1**) with aqueous sodium hydroxide solution gave the dihydroxyethers **2** in an unoptimised yield of 63% (Scheme 1). Methacrylic acid-d_5 (**4**) was then reacted with **2** in the presence of *p-Ts*OH in benzene to form nonaethyleneglycol dimethacrylate-d_{10} (**5**) in 75% with >21.7% deuterium incorporation of the average entire molecule. Other procedures including the method of *Mukayama* [20] or the use of the acid chloride of **4** in toluene and pyridine or triethylamine as base were either unsuccessful or gave poor yields. Deuterated *bisGMA* (**7**) was also prepared from methacrylic acid-d_5 (**4**) when diglycidyl ether of bisphenol-A (**6**) was stirred with **4** at 100°C for 6 h in the presence of Ph_3P and Ph_3Sb (Scheme 2) [20].

Experimental

All reactions were carried out under N_2. ^1H NMR (δ, ppm, with $SiMe_4$ as an internal standard) and ^{13}C NMR spectra (δ, ppm) were recorded on a Varian Gemini 200 spectrometer at 200 MHz and 50.3 MHz. FTIR spectroscopy was performed with thin films between KBr disks, using a Perkin Elmer 1700 instrument. Column chromatography was performed using Merck Si-60 (40–63 mm) silica gel. Petroleum spirits is the fraction distilled between 30–40°C. Acetone-d_6 and D_2O were purchased from Acros Organics.

Hydrolysis of Nonaethyleneglycol Dimethacrylate (**1**)

Nonaethyleneglycol dimethacrylate (**1**, 8.2 g, 14.9 mmol) (Nippon Oil and Fats, Japan) was stirred with an aqueous solution of 4.8 g NaOH (120 mmol) in 10.5 g water and 4.2 g methanol at room temperature for 1 h. The reaction mixture was diluted with 17.5 g water and stirred for a further 24 h at room temperature. Extraction with 2×20 cm^3 CH_2Cl_2 followed by drying the organic extract ($MgSO_4$) and evaporation of the filtered solution on the rotary evaporator gave a viscous oil of a mixture of oligoethyleneglycols **2** in an unoptimised yield of 3.8 g (62.9%). ^{1}H NMR ($CDCl_3$): $\delta = 3.45$ (s, 28H), 3.55 (s, 2×OH), 3.55 (dd, $J = 4.5$, 4.5 Hz, 4H), 3.85 (dd, $J = 3.5$, 5.0 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 72.05$ (2 CH_2), 69.92 (12 CH_2), 69.69 (2 CH_2), 60.87 (2 CH_2) ppm.

Cyanohydrin of Acetone-d_6; 2-Hydroxy-2-(methyl-d_3)-propanenitrile-3,3,3-d_3 (**3**)
Acetone-d_6 (18.5 g, 0.289 mol) was added to a solution of 21.0 g KCN (0.322 mol) in 20 cm^3 D_2O at 0°C within 1 min. Glacial acetic acid (22.0 g, 0.369 mol) was added to this mixture within 30 min and the exothermic reaction was kept in control by cooling the reaction mixture in an ice-H_2O bath. After another 30 min stirring at 0°C, the viscous solution was extracted with 2×50 cm^3 diethyl ether, and the combined ether layer washed with 20 cm^3 D_2O and then dried ($MgSO_4$). The organic solution was filtered and the solvent removed by rotary evaporation to give 24.0 g **3** (90.3%). ^{13}C NMR ($CDCl_3$): $\delta = 122.77$ (CN), 64.17 (*C*), 27.00 (*C*D_3).

(2-Methyl-d_3)-2-propenoic-3,3-d_2 Acid (**4**)
Concentrated H_2SO_4 (40 g, 0.408 mol) was treated with 5.0 g P_2O_5 (0.0176 mol) at room temperature within 5 min, and the temperature of the reaction mixture was then raised to 85°C and the mixture was treated with 1.0 g hydroquinone (9.08 mmol). Crude cyanohydrine of acetone-d_6 (24.0 g, 0.260 mol) was added to the reaction mixture over a period of 30 min and the exothermic reaction was monitored such that it did not go beyond 90°C. After the addition the temperature was raised and kept for 45 min at 120°C for complete dehydration. The mixture was then cooled to 95°C and treated with 40 cm^3 deionised water and kept for 3 h at that temperature for the hydrolysis step. The mixture was cooled to room temperature, mixed with 100 g silica gel, and chromatographed over 200 g silica gel with diethyl ether:petroleum spirits as eluent to give 10.5 g crude methacrylic acid-d_5 (44.2%). For further purification, the crude product was re-chromatographed over 50 g silica gel to give 7.1 g pure methacrylic acid-d_5 (29.9%) [17]. To enhance purity, this product was bulb-to-bulb distilled at 20 mm vacuum with an oven temperature at 140°C. The receiver flask contained a crystal hydroquinone to curb polymerization and 5.1 g very pure methacrylic acid-d_5 (**4**, 21.5%) with 98.6% deuterium incorporated was collected and was stored in the freezer. ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 173.43$ (*C*=O), 135.60 (*C*=), 127.33 (D_2*C*=), 16.90 (*C*D_3) ppm; ^{1}H NMR ($CDCl_3$): $\delta = 12.2$ (s, 1H) ppm. Residual peaks of the undeuterated methacrylic acid (all <1.4%) at $\delta = 1.99$, 5.57, 6.13 ppm.

Nonaethyleneglycol Dimethacrylate-d_{10} (**5**)
The oligoethyleneglycols (2.0 g, 4.825 mmol) were dissolved in 100 cm^3 benzene [22] containing 0.4 g hydroquinone (3.63 mmol) to curb polymerization and 0.5 g *p*-toluenesulfonic acid (2.9 mmol) as the catalyst. Methacrylic acid-d_5 (1.7 g, 18.66 mmol) was added to the mixture in one batch and the reaction mixture stirred at reflux for 24 h under N_2. The H_2O was collected with a *Dean-Stark* trap. The reaction mixture was cooled to room temperature and benzene removed by rotary evaporation. The viscous oil was chromatographed on 75 g silica gel and eluted with 100% diethyl ether to remove unreacted methacrylic acid-d_5, *p*-toluenesulfonic acid, and hydroquinone. Further chromatography with diethyl ether:acetone (9:1) eluted a series of oligoethyleneglycol dimethacrylates-d_{10} (ethyleneglycol units between $n = 4$ to $n = 10$) until the appearance of unreacted nonaethyleneglycol became apparent. All dimethacrylate fractions were combined as one fraction to give 2.05 g nonaethyleneglycol dimethacrylate-d_{10} (**5**, 75.8%). ^{1}H NMR ($CDCl_3$): $\delta = 3.64$ (sm, 28H), 3.74 (dd, $J = 4.9$, 4.9 Hz, 4H), 4.30 (dd, $J = 4.8$, 4.9 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 166.72$ (*C*=O), 135.37 (*C*=), 125.18 (D_2*C*=), 70.04 (O–*C*H_2, 14×), 68.58 (C(=O)O–*C*H_2), 63.33 (C(=O)O–CH_2–*C*H_2), 17.30 (*C*D_3) ppm.

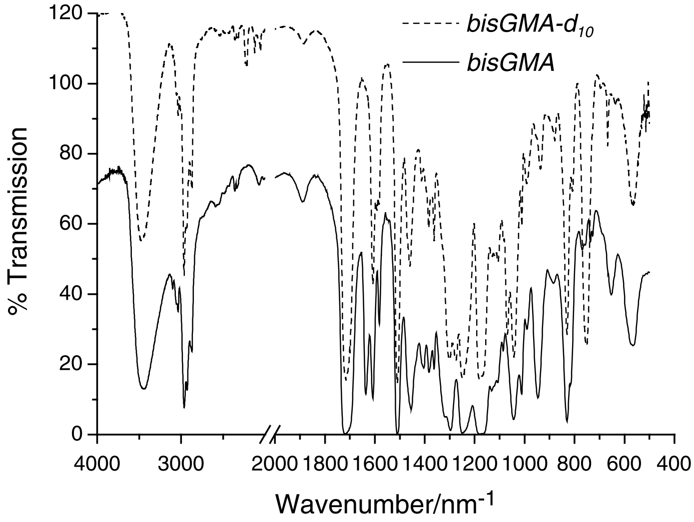


Fig. 1. Comparison of FTIR spectrum for *bisGMA* dimethacrylate and *bisGMA* dimethacrylate-d_{10} (**7**)

bisGMA Dimethacrylate-d_{10} (**7**)

Following the method of *Doyle et al.* [21], 5.68 g diglycidyl ether of bisphenol-A (**6**, 14.9 mmol) [23] supplied by Ciba Geigy as Araldite GY-9708-1 ($MW = 372$ g/mol) were stirred with a 10% mol equivalent excess of methacrylic acid-d_5 (**4**, 2.00 g, 21.9 mmol) at 100°C for 6 h in the presence of 0.15 wt% triphenyl phosphine and 0.45 wt% triphenyl antimony at which time, the FTIR peak at 915 cm^{-1} due to the oxirane ring had disappeared. The monomer was then purified by dissolution in $CHCl_3$ followed by extraction with 10% aqueous Na_2CO_3 solution and then vacuum stripping of the solvent. As expected, the FTIR spectrum of **7** was very similar to that of *bisGMA* except for the absence of the peak at 1635 cm^{-1} associated with the $=CH_2$ stretch of the methacrylate group in *bisGMA* (see Fig. 1).

Acknowledgements

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[17] CAUTION: Pure methacrylic acid is known to decompose exothermically and therefore needs to be inhibited with e.g. hydroquinone monomethyl ether.
[18] Although patented literature is available about the use of methacrylic acid-d_5, the synthesis is either difficult or dangerous [19] or literature is obscure to retrieve or has too little experimental details
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[21] Doyle TE, Fekete F, Kernan PJ, Plant WJ (1967) US Pat 3,317,465
[22] CAUTION: Benzene is a carcinogen suspect agent. The authors recommend that toluene should be used instead
[23] Note that *DGEBA* contains oligomers raising its molecular weight to 380 g/mol. The average structure of *DGEBA* is given as in Scheme 2