Synthesis and Characterization of a Monofunctional Analog to BIS-GMA: A Dental Monomer

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SYNOPSIS

A new monofunctional BIS-GMA monomer, 4-(2-phenyl isopropyl)-3-phenoxy-2-hydroxy propyl methacrylate (monofunctional-BIS-GMA, hereafter abbreviated as MF-BIS-GMA) was synthesized as an adduct of 4-cumylphenol and glycidyl methacrylate for use as a dental monomer. The new monomer was characterized by FTIR, ^{1}H, ^{13}C (attached proton test, APT), UV, HPLC, and GPC. The viscosity and solubility of the new resin are also presented. The results were compared with the difunctional analog, BIS-GMA (2,2-bis[4-(2-hydroxy-3-methacryloyloxypropoxy)]phenyl propane), which is commercially available and currently used in dental restorative materials. Both monomers were light-cured using 0.3% camphorquinone and 0.75% 2-(dimethylamino)ethyl methacrylate as photoinitiators. The extent of monomer conversion and the potential for residual monomer leachability were compared between the two cured resins. The monofunctional resin was found to yield higher monomer conversion values (74 vs. 39%) and lower leachable components (0.03 vs. 30.6 mol %) than those of the difunctional analog. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

In general, methacrylate-based monomers are used extensively in dental composites, bonding resins, sealants, and dentin-adhesive systems. Ever since Bowen[1,2] developed BIS-GMA (2,2-bis[4-(2-hydroxy-3-methacryloyloxypropoxy)]phenyl propane), a resin synthesized from bisphenol A and glycidyl methacrylate (GMA), as a matrix in dental composites, most of the commercial dental restorative polymer products contain this compound. BIS-GMA has a rigid aromatic backbone which leads to lower polymerization shrinkage. However, light-cured BIS-GMA-based materials possess a low degree of monomer conversion due to restriction in segmental motion of this highly viscous, bulky molecule and entrapped, unreacted monomer species. Hence, poor monomer conversion as well as relatively high amounts of unreacted, leachable monomer in the resulting composite affects both the mechanical and biocompatible properties of ultimate restoration.[3-6]

The structural effect of different aromatic dimethacrylates on mechanical properties was well narrated and compared with BIS-GMA by Kawaguchi et al.[7,8] They concluded that ethoxylation and fluorination of BIS-GMA reduces water sorption and slightly decreases the mechanical properties of the cured product due to the segmental mobility of their side chains. However, all compounds examined were difunctional in nature and no attempt was made to compare the extent of monomer conversion or reduction in the amount of leachable materials as compared to the standard product.

It would be of great interest to synthesize an aromatic monomethacrylate BIS-GMA equivalent (MF-BIS-GMA) and study its structural effect on monomer conversion. The hypothesis tested would be that the monofunctional moiety would yield a higher extent of attachment to the polymer network, yielding both greater overall monomer conversion while also reducing the extent of uncured, leachable product.

The objectives of the present study were to

1. Develop methods of synthesis and characterization of 4-(2-phenyl isopropyl)-3-phenoxy 2-hydroxy propyl methacrylate (MF-BIS-GMA), and
2. Compare monomer conversion and the mol % of leachable components of monofunctional and difunctional BIS-GMA.

EXPERIMENTAL

Materials

The materials required for synthesis of MF-BIS-GMA were as follows: 4-cumylphenol (4CP) (Aldrich, lot 04426BT), glycidyl methacrylate (GMA) (Aldrich, lot 00403DY), 4-methoxyphenol (Aldrich, lot 08426CZ), N,N-dimethyl-p-toluidine (DMPT) (Aldrich, lot 05804TT), 2-(dimethylamino)ethyl methacrylate (DMAEMA) (Aldrich, lot 05030LY), sodium hydroxide (Fisher, analytical grade), methylene chloride (Fisher, HPLC grade), chloroform (Fisher, HPLC grade), silica gel (J. T. Baker Chemical Co., Jackson, TN, 40-140 mesh), and hexane (Fisher, HPLC grade). All materials were used as received.

Methods

Synthesis of MF-BIS-GMA Resin

A calculated amount of 4CP, GMA, and the catalyst was added to a three-necked flask fitted with a water condenser, nitrogen inlet, and thermometer. Two different catalysts were used to test for maximum reaction efficiency: DMPT and DMAEMA. The reactant ratio of 4CP and GMA was also modified along with the catalyst type to determine the ideal conditions for synthesis. To prevent spontaneous polymerization, 4-methoxyphenol (60 ppm) was added. The three-necked setup was fixed in a heating mantle which was controlled by a rheostat to maintain the temperature of the mixture ($60 \pm 2°C$). The mixture was magnetically stirred under a purified nitrogen blanket until the reaction was complete.

FTIR spectroscopy (FTS-40, Digilab Division of Bio-Rad, Cambridge, MA) was used to monitor the ring-opening reaction of the epoxy group as inferred by the disappearance of the absorption peak at 903 cm^{-1}, characteristic of an epoxide group.[9,10] The method involved withdrawal of aliquots and placing them on a KRS-5 ATR plate (Harrick Scientific, Ossining, NY). Infrared spectra were obtained using

eight scans at a resolution of 2 cm^{-1}. The extent of etherification was monitored by taking the ratio of absorbance intensity of end epoxide at 903 cm^{-1} and the absorbance intensity of vinyl, $C{=}C$ group at 1637 cm^{-1}, which acted as an internal standard.

From this ratio, the degree of reaction conversion was calculated:

% Epoxide concentration

$$= \frac{\text{reaction at time } t}{\text{reaction ratio at time zero}} \times 100\% \quad (1)$$

Degree of reaction conversion

$$= (100\% - \text{epoxide concentration}) \quad (2)$$

Table I displays the reaction process using two different catalysts for the synthesis.

Purification of the reaction product was accomplished by dilution with methylene chloride and washing with 5% NaOH and 2.5% HCl, followed by distilled water. The product was dried using anhydrous potassium carbonate overnight. Purified resin was recovered from methylene chloride solvent using a rotovapor. Resin was further purified by column chromatography (silica gel, eluent: chloroform/hexane, 50/50 v/v).

Characterization

The viscosity of the synthesized resin was measured by a Ubbelohde capillary viscometer (Schott Gerate, Germany) with a viscometer constant [$(k) = 1.098$]. The viscosity (cps) is expressed by

Viscosity = flow time (s) $\times k$

$$\times \text{resin density } (1.10545) \quad (3)$$

The viscosity of commercial BIS-GMA was measured using a viscometer (HB series cone/plate, CP-52 cone spindle, Brookfield Engineering Laboratories, Stoughton, MA) at 25°C.

The solubility of MF-BIS-GMA and BIS-GMA were tested in the following solvents: chloroform, methylene chloride, acetone, ethyl acetate, methyl ethyl ketone, dimethylformamide, methanol, ethanol, benzene, hexane, and dimethyl sulfoxide. Determination of solubility was performed using visual observation of the presence of a resin/solvent interface after vigorous hand-mixing.

^{1}H- and proton-decoupled ^{13}C-NMR spectra of MF-BIS-GMA and commercial BIS-GMA resins were acquired using a Varian XL-300 (FT) spec-

Table I   Epoxide Conversion During Synthesis

Time (h)	Reaction with 2% DMPT		Reaction with 2% DMAEMA	
	Reaction Ratio	% $R \times n$ Conversion	Reaction Ratio	% $R \times n$ Conversion
0.5	1.663		1.181	
1	1.463	12.03	0.911	22.86
2	1.173	29.50	0.727	38.44
3	0.827	50.30	0.541	54.19
4	0.621	62.70	0.504	57.32
5	0.218	86.90	0.418	64.61
6	0.160	90.38	0.304	74.26
7	0.114	93.14	0.213	81.96
8	0.052	96.87	0.183	84.50
9	0.033	98.02	0.089	92.46
10	−0.061	100.00	0.073	93.82
12			−0.019	100.00

trometer operated at 300 MHz. $CDCl_3$ solvent with 1% tetramethylsilane as the internal standard was used for qualitative analysis. UV spectra of MF-BIS-GMA and BIS-GMA resins were obtained using a Shimadzu UV 160U, wavelength 200–400 nm, in methylene chloride solution.

The presence of isomers in BIS-GMA and MF-BIS-GMA was analyzed by HPLC (Model 110 A pump and Model 334 analytical UV detector at 254 nm, Beckman Instruments, Berkeley, CA). The following conditions were used: column: Supelcosil LC 18, Supelco, Bellefonte, PA; solvent system: 70/30 (v/v) methanol/water; and flow rate: 1 mL/min. HPLC tracings were integrated using a SMAD II Integrator/DA system and SMAD Chrom v2.2 software (Morgan Kennedy Research, Guilford, CT).

GPC of both resins was performed using a Waters M-45 solvent delivery system, Shimadzu SPD-6AV UV-VIS spectrophotometric detector. Waters Ultrastyragel 500 Å THF column (part 10571), and Waters Ultrastyragel 104 Å THF column (part 10573) using THF as the mobile phase and a 1 mL/min flow rate.

Photopolymerization of Monofunctional and Difunctional BIS-GMA Resins

Photopolymerization of both the purified synthesis product and commercial BIS-GMA (lot 307-45-1, Esschem, Essington, PA) was carried out using 0.3% camphorquinone (lot 0201LP, Aldrich Chemical Co., Milwaukee, WI) as the photoinitiator and 0.75% DMAEMA as the photoactivator, under visible light (Triad II light-curing unit, Dentsply, York, PA). The extent of monomer conversion of thin-film specimens was calculated by FTIR using published procedures.[9]

Determination of Leachable Products in Monofunctional and Difunctional BIS-GMA Resins

Photopolymerization of the resins was performed as described above. The cured specimens were weighed and then placed in THF. HPLC was used to quantify the proportion of unreacted monomer leaching from each of the two cured resin products.

Table II   Synthesis Conditions and Resin Properties

Reactant Ratio (4CP : GMA)	2% Amine	Yield (%)	Time (h)	Isomer (%)[a]	
				Linear	Branched
0.8 : 1.0	DMPT	75	10	84	16
0.8 : 1.0	DMAEMA	66	12	77	23
1.0 : 1.0	DMAEMA	67	12	90	10

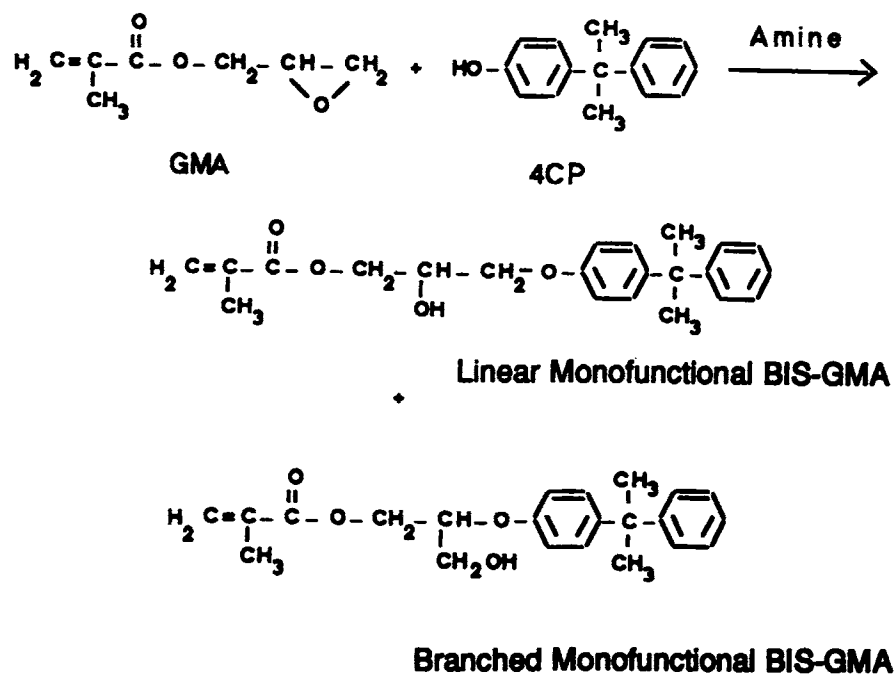[a] Obtained from HPLC data.

Figure 1 Synthesis scheme for monofunctional BIS-GMA.

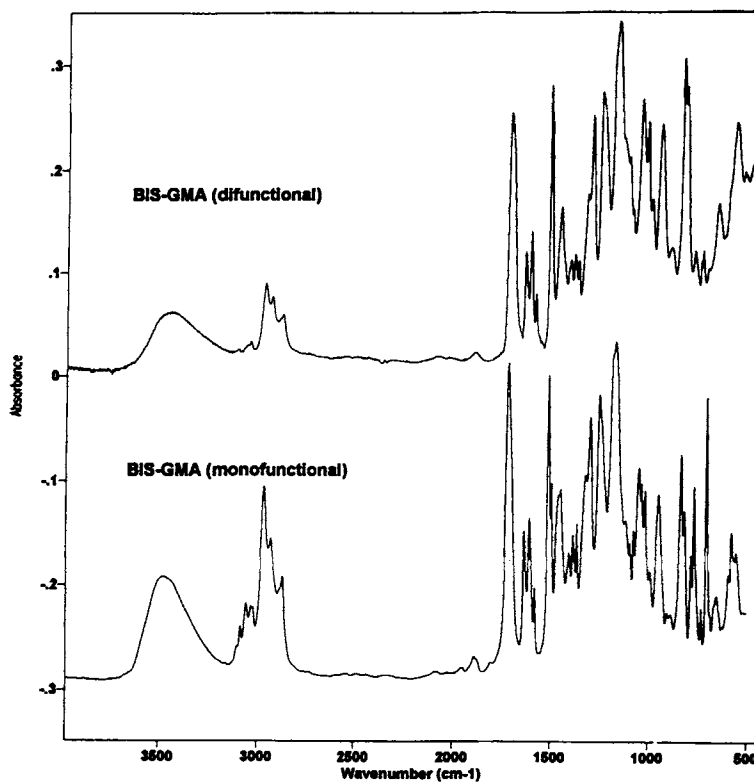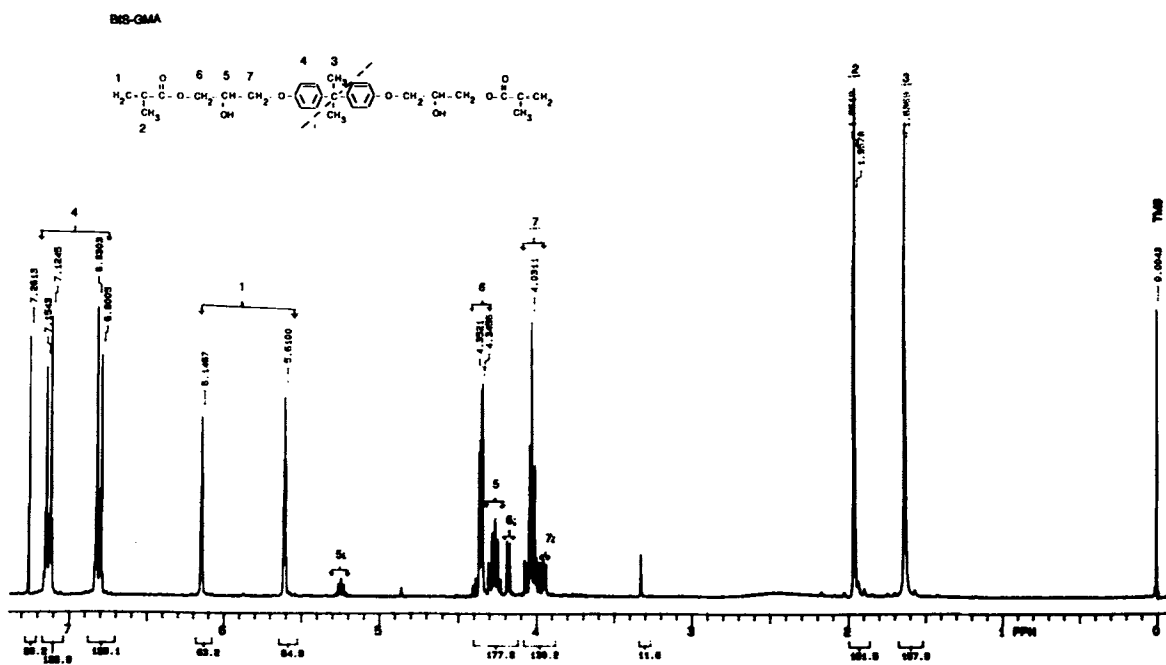**Figure 2** FTIR spectra of monofunctional and difunctional BIS-GMA.

Figure 3 ¹H-NMR spectrum of BIS-GMA.

RESULTS AND DISCUSSION

Monomer Synthesis

In previous literature, the reaction between epoxide and phenolic hydroxyl groups was carried out in the presence of the NaOH catalyst in higher boiling solvents like toluene or xylene.[11,12] However, this reaction was found to lead to poor conversion due to polymerization of the product. Use of tertiary amine catalysts, such as DMPT,[13] triethylamine, and triethylbenzylammonium chloride,[8,14] have been found to be more effective for addition etherification of glycidyl esters of unsaturated acids to bisphenols. In the present synthesis, two different tertiary amine catalysts, DMPT and DMAEMA, were used in the preparation of MF-BIS-GMA.

Table I indicates that the course of the reaction was a smooth addition etherification and yielded 100% reaction conversion of the epoxide group. The use of DMPT demonstrated a faster reaction rate than did the use of DMAEMA.

Table II summarizes different synthesis conditions and resin properties. When the reactants are used in similar proportions, DMPT is found to provide a higher product yield and lower amount of branched isomer. Use of a higher DMAEMA reactant ratio is found not to affect the product yield, but the proportion of linear isomer is greatly increased. Ring opening of the epoxide group has

probabilities of opening into either linear or branched isomers or both (Fig. 1). This condition has also been observed in the case of acid or anhydride reaction with epoxide.[10,15] DMPT reduces the branched isomer in the product; however, the color is more important when the resin is used as a matrix in an esthetic dental polymer. DMAEMA was found to be the most effective catalyst to improve the yield of the desired linear isomer when it was used with a 1 : 1 reactant ratio. The yield of branched isomer was found to depend strongly upon synthesis conditions. Thus, the catalyst of choice for purposes of dental application was DMAEMA at a reactant ratio of 1 : 1 4CP/GMA.

The resin was purified by a 5% NaOH wash to remove excess 4CP. It was found that even after a multiple alkali wash 4CP was not removed totally from the product. The reason for this condition was not apparent. Prolonged stirring with the alkali solution led to cleavage of the ester group. The total elimination of 4CP from the resin product was greatly facilitated through chromatographic purification.

Characterization and Comparison of Both Monofunctional and Difunctional BIS-GMA Resins

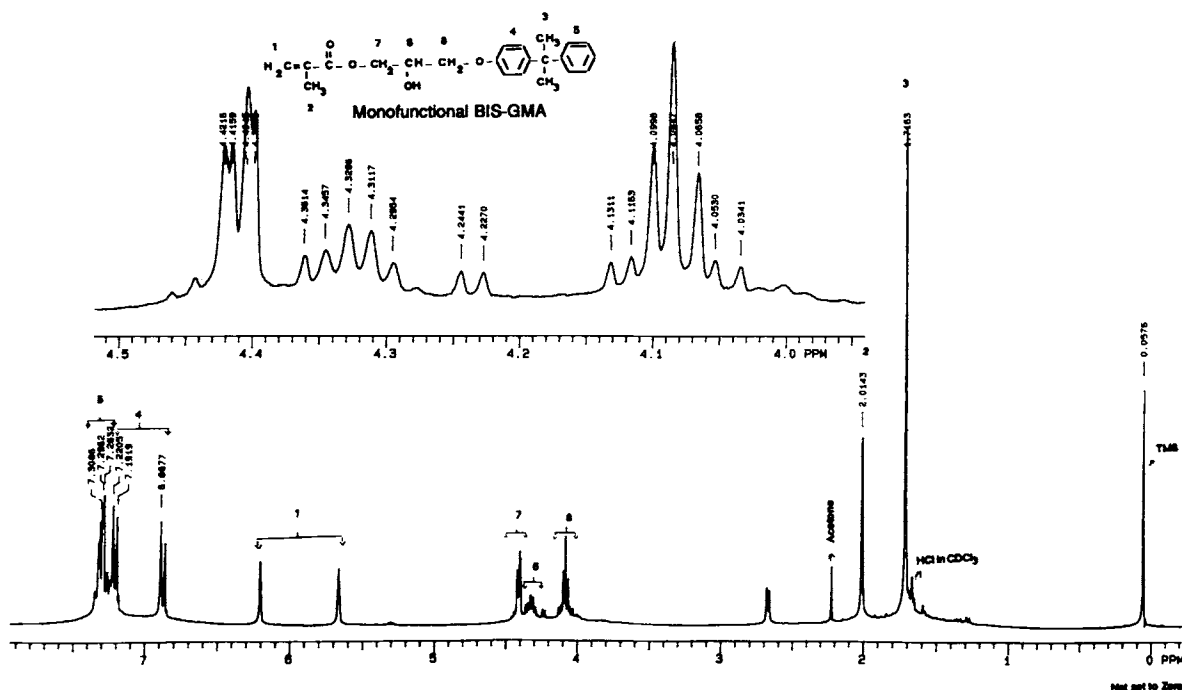The chromatographically purified, synthesized resin was clear and colorless. The viscosity was deter-

Figure 4 ¹H-NMR spectrum of monofunctional BIS-GMA.

mined to be 1072 ± 20 cps. As stated from the manufacturer, the viscosity of commercial BIS-GMA was approximately 530,000 cps. Both monomers were found to be soluble in all solvents tested with the exception of hexane and benzene.

The MF-BIS-GMA was analyzed by techniques, such as FTIR and NMR, to confirm its structure as 4-(2-phenyl isopropyl)-3-phenoxy-2-hydroxypropyl methacrylate and to compare it with commercially available BIS-GMA, which has an identical structure, but is in a dimethacrylate form.

The FTIR spectra (Fig. 2) show both mono- and dimethacrylate forms of BIS-GMA. The spectrum of the synthesized monomethacrylate demonstrates the disappearance of the terminal epoxide absorption at 903 cm⁻¹. Other characteristic peaks at 1717 cm⁻¹ (C=O), 1637 cm⁻¹ (C=CH₂, stretching), 943 cm⁻¹ (C=CH₂, bending), and 3400 cm⁻¹ (—OH) are identical to both forms of BIS-GMA. However, characteristic absorptions of MF-BIS-GMA due to the monosubstituted phenyl group[16] are observed at 1494, 1446, 1072, and 1030 cm⁻¹ (in-plane CH bending), at 781 and 762 cm⁻¹ (in-phase CH wagging), and at 699 cm⁻¹ (out-of-plane ring bending). These characteristic absorptions confirm its structure as presented in Figure 1.

The structure of the monomethacrylate and its isomer were also identified from NMR data. The

¹H-NMR spectra of mono- and dimethacrylate forms of BIS-GMA are given in Figures 3 and 4. The chemical structure of commercial BIS-GMA exists as a mirror image of one side and showed seven different types of protons[15] corresponding to its structure (Fig. 3). In addition to these seven types of protons, (labeled as 1, 2, 3, 4, 7, 6, and 8 in Figs. 3 and 4), the monomethacrylate form showed a multiplet at ∂ = 7.13 to 7.30 due to free phenyl protons. Since the TMS value is not set at zero, 0.0576 must be subtracted from the free phenyl proton value. The structural isomers of the dimethacrylate form of BIS-GMA have been well documented elsewhere.[15] The presence of a branched isomer is demonstrated as a quintet at δ = 5.23 ppm (Fig. 3) due to a tertiary methine proton (—CH—). Doublets at δ = 3.97–4.1 ppm and at δ = 4.16–4.18 ppm, corresponding to the methylene protons (—C—CH₂—OH and Ar—O—CH₂—), also confirm the branched isomer form. Only traces of these groups can be noted in the MF-BIS-GMA product (Fig. 4).

¹³C-NMR spectra of mono- and dimethacrylate BIS-GMA (Figs. 5 and 6) provide additional evidence of the structural isomers of these resins. The characteristic ¹³C chemical shifts corresponding to particular carbon atoms (identified from standards of starting materials) numbered from 1 to 13 are
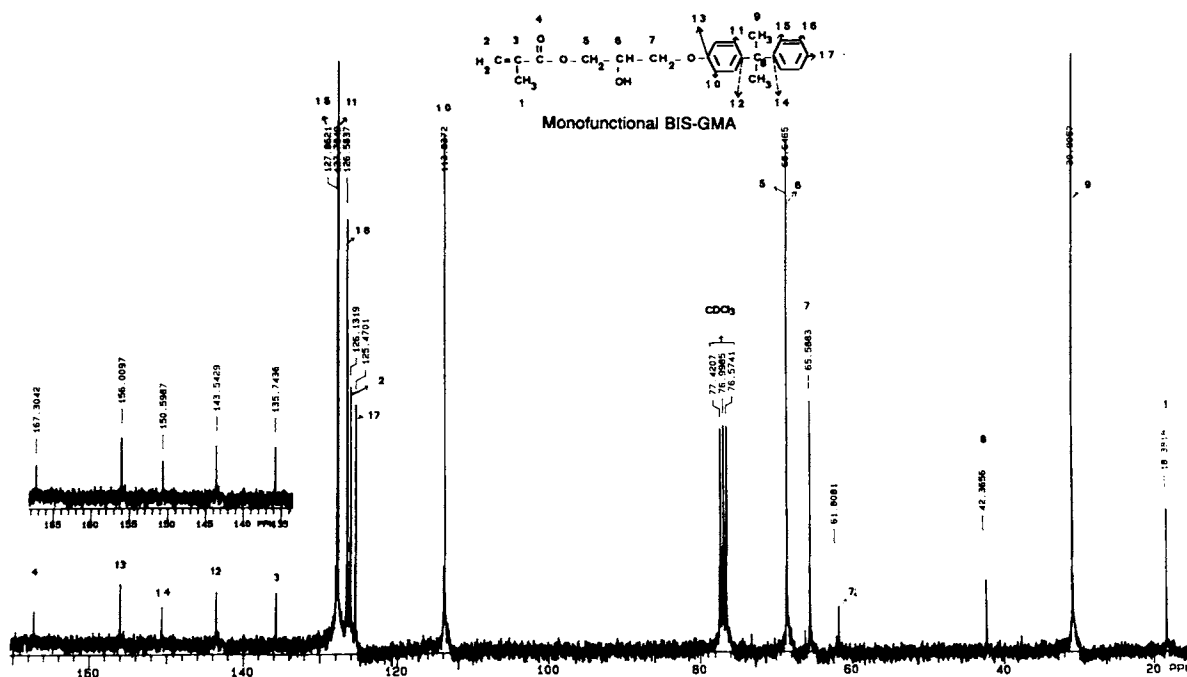
Figure 5 ^{13}C-NMR spectrum of monofunctional BIS-GMA.

noted at the same frequency for both resins. ^{13}C chemical shifts belonging to branched isomer carbons of both resins [—CH(CH$_2$— OH) —CH$_2$—] are numbered as C5i, C6i, and C7i. These shifts can be seen better in BIS-GMA than in the MF-BIS-GMA product due to the low concentration of the sample used to obtain the spectra. Four distinguishing aromatic ^{13}C chemical shifts of the MF-BIS-GMA resin arising from the free phenyl group (C14 at 150.60 ppm, C15 at 127.86 ppm, C16 at 126.59, and C17 at 125.47 ppm) are observed in Figure 5.

^{13}C-APT spectra show a clear picture of various ^{13}C chemical shifts such as primary, secondary, tertiary, and quaternary carbons. In the ^{13}C-APT spectrum of MF-BIS-GMA (Fig. 7), primary (C1 and C9) and tertiary (C6, C10, C11, C15–C17) ^{13}C chemical shifts are observed on the upper level of the graph. On the lower level, secondary (C2, C5, C7, C7i) and quaternary (C3, C4, C12, C13, C14) ^{13}C chemical shifts are observed. In Figure 8, this relationship is inverted for BIS-GMA. Additional aromatic ^{13}C chemical shifts due to free phenyl carbons of the MF-BIS-GMA material such as C14 (quaternary carbon, at lower level), and C15–C17 (tertiary carbon, at upper level) are noticed in Figure 7. It should be stressed that the carbon atom location numbers (as noted above) in reference to Figures 7 and 8 pertain to similar carbon atom locations within each molecule.

UV spectra of both the mono- and dimethacrylates are presented in Figures 9 and 10, respectively. A strong intense band at λ_{max} = 231 nm is attributed to the C $=$ C double bond (π-π^* transition) conjugated with the carboxyl group (n-π^* transition).[17] A characteristic low-intensity band of multiple absorptions centered around 276 nm corresponds to the π-π^* transition of aromatic groups of MF-BIS-GMA[17] (Fig. 9). Both strong and weak bands due to methacrylate and aromatic groups at λ_{max} = 233 and 277 nm, respectively, are observed in BIS-GMA (Fig. 10).

Three-dimensional GPC spectra (absorption vs. wavelength vs. retention time) of MF-BIS-GMA and BIS-GMA are seen in Figures 11 and 12, respectively. They both show a strong, sharp peak and a weak, broad peak on the wavelength axis. A slight shoulder in the BIS-GMA resin (Fig. 12) is observed with the strong peak toward a lower retention time: the higher molecular weight region. This shoulder indicates the presence of an oligomer in BIS-GMA which is not seen in the monofunctional equivalent (Fig. 11). The absence of this shoulder proves that the synthesized resin is pure, with a single molecular weight. The recorded retention time for both di- and monofunctional resins are 18.78 and 19.43 min, respectively.

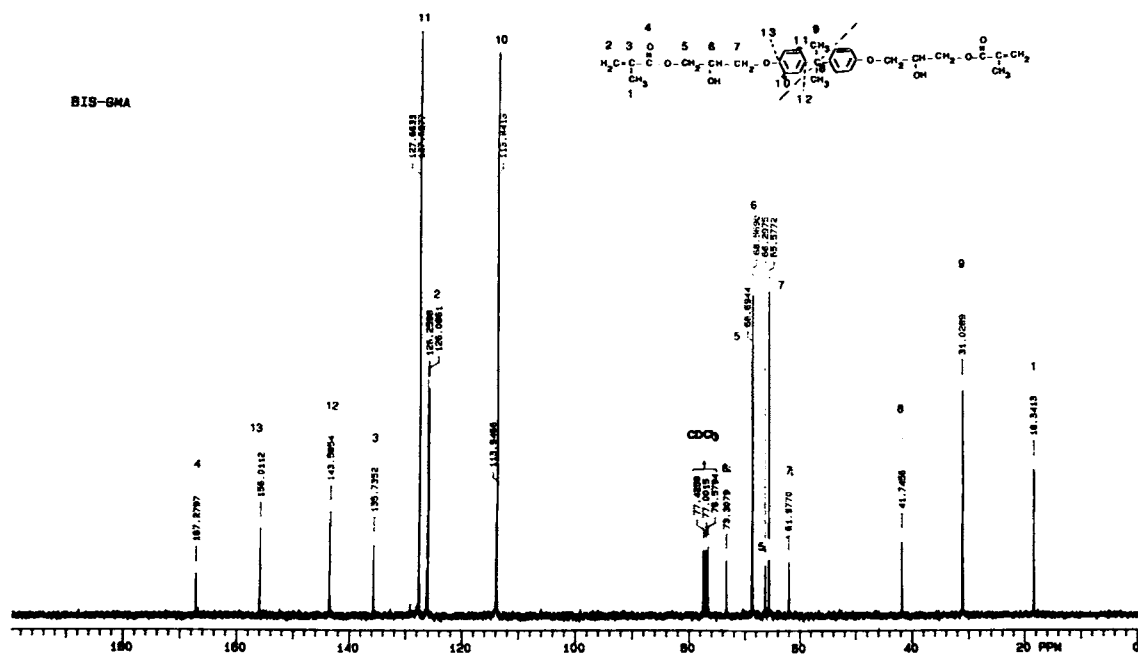The presence of linear and branched isomers is also confirmed by HPLC data [Fig. 13(A) and (B)].

Figure 6 ¹³C-NMR spectrum of BIS-GMA.

The branched isomer in both cases eluted first at a lower retention time (14.32 and 10.51 min for MF-BIS-GMA and BIS-GMA) than did the linear isomer (43.82 and 32.32 min for MF-BIS-GMA and BIS-GMA). Figure 13(B) indicates the presence of the linear/branched isomer of the difunctional monomer, appearing as a peak at 25.81 min.

Monomer Conversion and Leachable Component in Polymers

Table III presents the results of the relative monomer conversion of the monofunctional resin to that

of the difunctional analog as determined using FTIR. It can be seen that the monofunctional resin cured nearly twice as much as did the difunctional material (39 vs. 74%). This increase in conversion may be attributable to the differences in viscosity between the two resins. The viscosity of MF-BIS-GMA was found to be 1/500th that of its difunctional analog, BIS-GMA. The lower cure of BIS-GMA may also be the result of the inability of pendant methacrylate groups to react. Rigid aromatic rings would inhibit free rotation of these pendant groups from a configuration which is amenable to further reaction. The methacrylate group in MF-BIS-GMA is not under
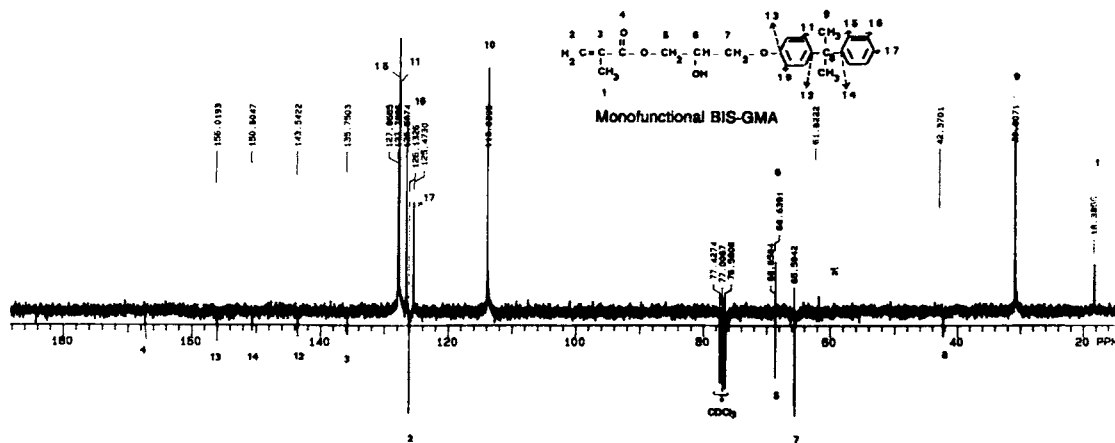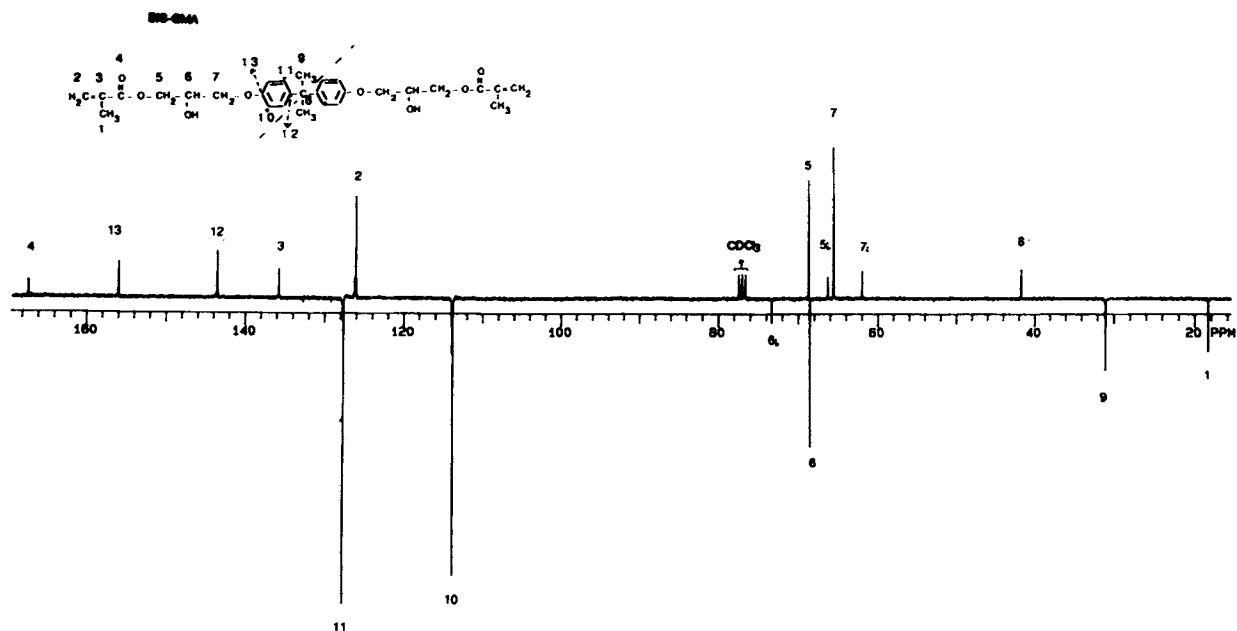

Figure 7 ¹³C-APT NMR spectrum of monofunctional BIS-GMA.

Figure 8 ³C-APT NMR spectrum of BIS-GMA.

such constraints and is able to react to a greater extent. Also, it is evident that the difunctional polymer leached more monomer (1000 times more) than did the monofunctional polymer. Again, the influence of the greater viscosity of the BIS-GMA monomer may be responsible for its inability to enter into a reaction, resulting in the greatly increased leachability.

The intent of the current research was to describe the synthesis, characterization, and photocuring potential of the monofunctional analog of the difunctional monomer, BIS-GMA. In that respect, the results of the polymerization of these two homopolymers are compared. In actual use, however, the difunctional monomer is commonly combined with another monomer which lowers the total viscosity

of the system and aids in increasing the overall monomer conversion. Further studies combining MF-BIS-GMA with the commonly used comonomer triethylene glycol dimethacrylate and comparing those results with those of the difunctional BIS-GMA moiety are currently underway.

CONCLUSION

The most favorable synthesis conditions for MF-BIS-GMA were determined to be the following: temperature 60°C, 1 : 1 ratio of reactants (4CP: GMA), and 2% by weight of DMAEMA as the amine catalyst. The structure of MF-BIS-GMA was confirmed by FTIR, NMR, UV, and GPC and matched
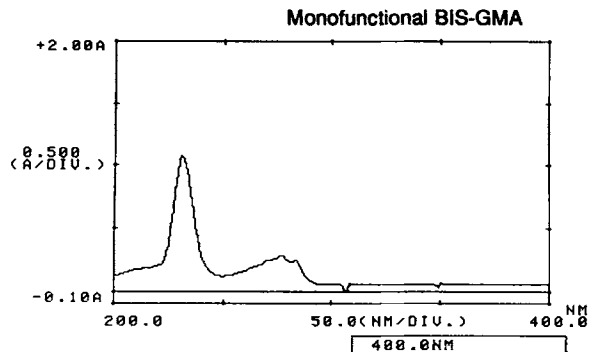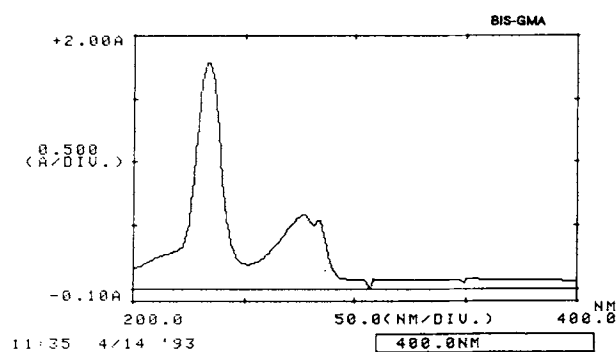

Figure 9 UV spectrum of monofunctional BIS-GMA.

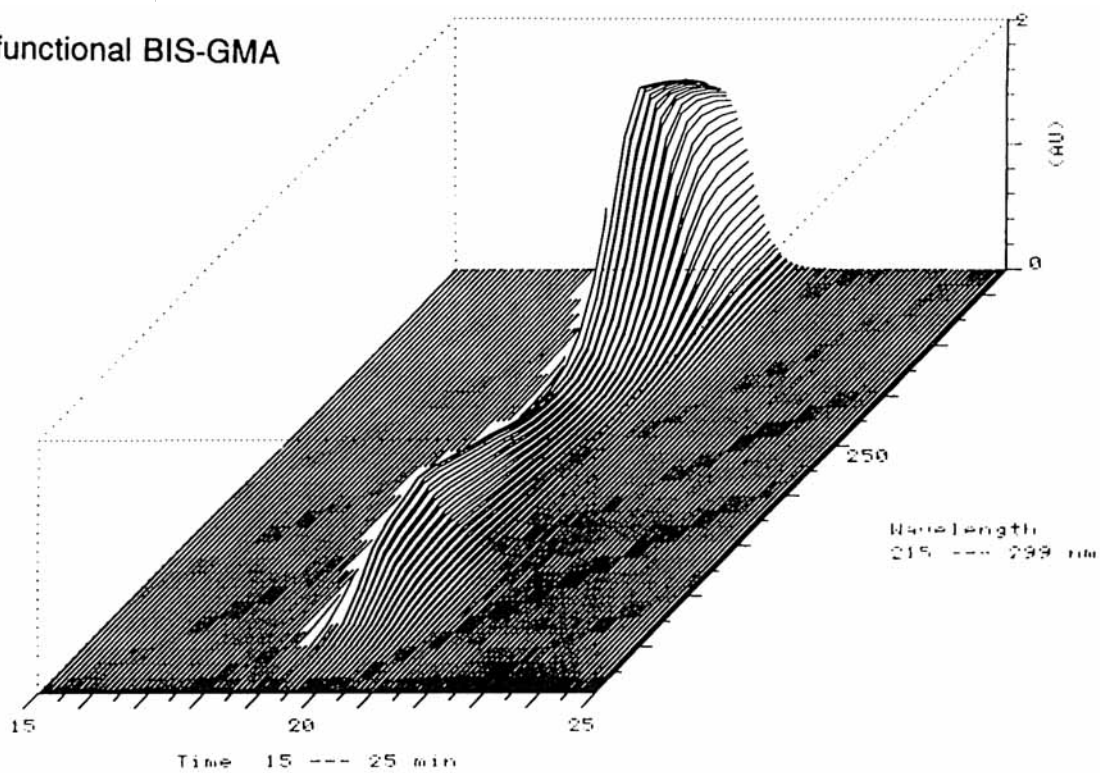**Figure 10** UV spectrum of BIS-GMA.

Monofunctional BIS-GMA

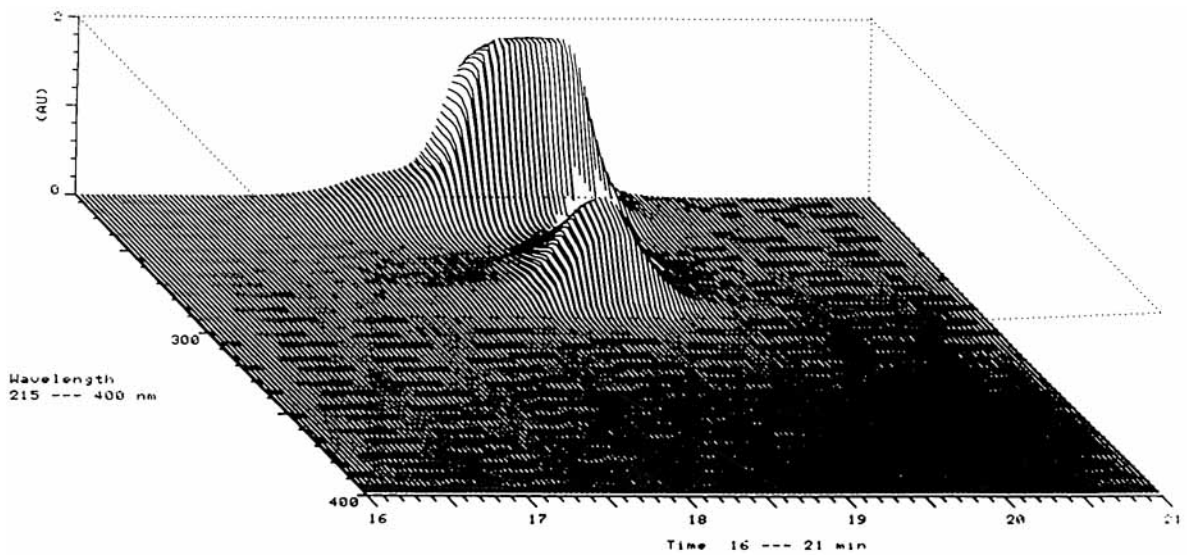**Figure 11**   GPC-3D spectrum of monofunctional BIS-GMA.

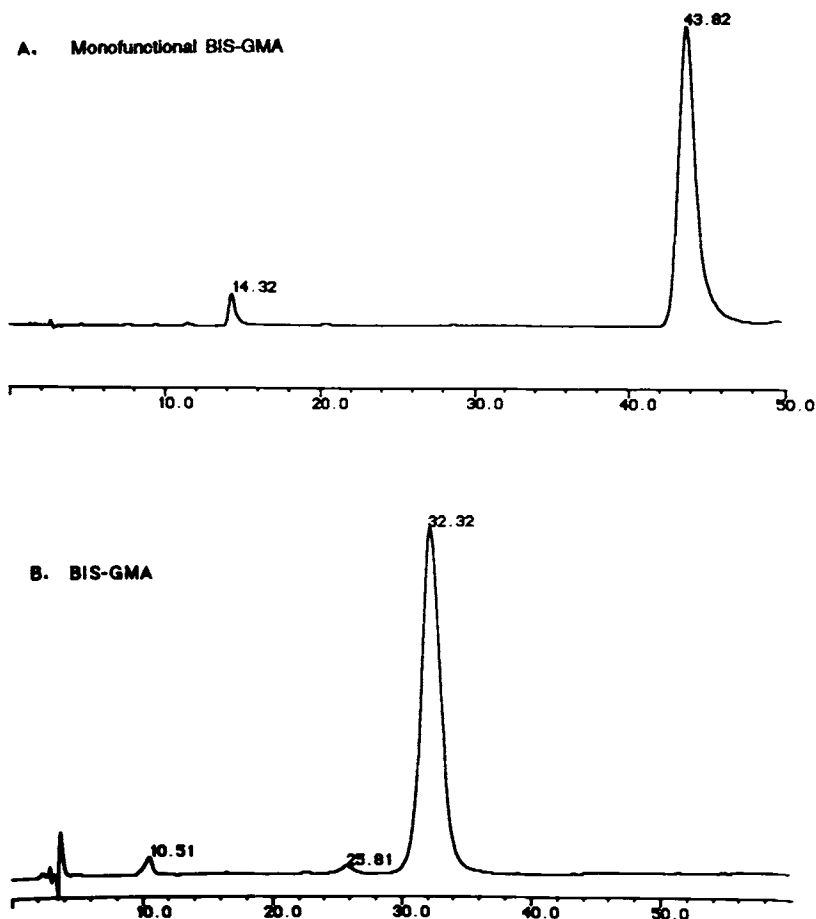**Figure 12**   GPC-3D spectrum of BIS-GMA.

Figure 13   HPLC of (A) monofunctional BIS-GMA and (B) difunctional BIS-GMA.

well with the commercial dimethacrylate form of BIS-GMA. Monomer conversion was improved in the homopolymer of MF-BIS-GMA over that seen with difunctional BIS-GMA. Also, the monofunctional resin remarkably demonstrated a less leachable component than did the difunctional material. It can be concluded that monofunctional BIS-GMA has a great potential for use as a dental restorative resin.

Table III   Monomer Conversion and Leachable Component

Monomer Type	Monomer Conversion (%)[a]	Leachable Component (mol %)[b]
MF-BIS-GMA	74.1 (1.8)[c]	0.03 (0.01)
BIS-GMA	39.3 (0.7)	30.6 (1.8)

[a] Calculated from FTIR data.
[b] Obtained from HPLC data.
[c] Mean of three replications (standard deviation).

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