Effect of Solvent Type on the Degradation of 4-MET

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This study sought to investigate the degradation mechanism of 4-methacryloyloxy ethyl trimellitic acid, 4-MET, which is commonly used as an acidic monomer in solvated self-etching primers or one-step bonding agents. To this end, we examined the effects of solvent type used — such as ethanol, methanol, and acetone — on the degradation mechanism of 4-MET by using the 13C NMR technique.

The degradation mechanism of 4-MET was strongly dependent on the type of solvent used. When an alcohol-based solution was used for 4-MET, the esterification of 1- or 2-carboxylic acid in 4-MET occurred. However, when an acetone solvent was used for 4-MET, the esterification reaction did not occur. Increases in the aging period of 4-MET solvated solutions resulted in the hydrolysis of the benzoyl ester portion in 4-MET. The 2-hydroxyethyl methacrylate, produced as a subproduct, also became hydrolyzed. In addition, methacrylic acid, non-esterified and esterified trimellitic acid, as well as ethylene glycol were produced as subproducts. In particular, the production of trimellitic acid and ethylene glycol affected the bonding efficacy and durability of the resin to the tooth created by self-etching primers or one-step bonding agents that contained the altered 4-MET.

Keywords: Acidic monomer, 4-MET, Degradation, 13C NMR

INTRODUCTION

It is common knowledge that the application of single bottle type self-etching primers or one-step bonding agents to the tooth promotes the bonding of resin to the tooth1,2,3. These primers and bonding agents consist of acidic, hydrophilic, and/or hydrophobic methacrylester monomers, and water as a solvent.

The 4-methacryloyloxy ethyl trimellitic acid, 4-MET, is commonly utilized in self-etching primers or one-step bonding agents. This is because it is a very useful and functional acidic monomer that enhances the bonding of the resin to the tooth. This enhanced bonding is possible since 4-MET not only permeates the smear layer and demineralizes both the intact enamel and dentin, but also primes the etched enamel and dentin4. In general, self-etching primers and one-step bonding agents that contain 4-MET are solvated by evaporable solvents, such as ethanol or acetone. This is necessary because the solubility of 4-MET in water is very poor.

In a study on the degradation mechanism of 4-MET, Fujita and Nishiyama employed an accelerated aging test to investigate self-etching primers — such as the UniFil Bond Primer (UB) — which contained 4-MET, 2-hydroxyethyl methacrylate (HEMA), water, and ethanol5,6. When UB was aged at 37°C, the 1- or 2-carboxylic acid in 4-MET became esterified by the ethanol during the beginning of the primer’s storage period. In addition, methacrylic acid (MA), ethylene glycol (EG), and trimellitic acid (TA) were produced as subproducts, due to the hydrolysis of the ester portion in 4-MET and/or HEMA. However, the principal degradation mechanism of 4-MET has not yet been identified.

It is very important to investigate the degradation mechanism of 4-MET utilized in solvated self-etching primers or one-step bonding agents. This is chiefly because the esterification of carboxylic acid in 4-MET results in decreased etching efficacy of the tooth components. In addition, MA, EG, and TA, which are produced by the hydrolysis of the ester portion in 4-MET, cause the quality of the hybrid layer — created by self-etching primers or one-step bonding agents containing the altered 4-MET — to deteriorate.

The objective of this study was to investigate the degradation mechanism of 4-MET employed in solvent-based self-etching primers or one-step bonding agents. To this end, we examined the effects arising from the types of solvent used, such as ethanol, methanol, and acetone, on the degradation mechanism of 4-MET.

MATERIALS AND METHODS

Materials

4-MET was provided by Sun Medical Co. (Gifu, Japan). Distilled deionized water was added to deuterium oxide. Consequently, 20 mass% deuterium oxide aqueous solution was used to prepare 70 vol%
solvated solutions by using ethanol, methanol, or acetone.

**NMR observation**

Three types of 70 vol% solvated solutions were prepared after adding 20 mass% deuterium oxide aqueous solution to ethanol, methanol, or acetone. A quantity of 100 mg of 4-MET was then dissolved in 1 ml of each solvated solution. Thereafter, these solutions containing 4-MET were aged at 40° C for 3, 5, 7, 10, or 14 weeks. At the completion of each aging period, 13C NMR observations on 4-MET were conducted by using an EX-270 spectrometer (JEOL, Tokyo, Japan) operating at 67.80 MHz and at 25°C. A 45° pulse was used for the NMR observations, with accumulation and repetition times at 2,000—5,000 times and 3.8 seconds, respectively. Resolution of the chemical shift of NMR peak was 0.009 ppm. Furthermore, as a control, 13C NMR spectra of 4-MET were observed after dissolving 4-MET in each of the 70 vol% solvated solutions and allowing these samples to stand for one hour (aging period: 0 days). Hexamethyl-disiloxane (HMDSO) was used as an external reference. Each experiment was conducted twice.

**RESULTS**

**Degradation mechanism of 4-MET in alcohol solutions**

Figure 1 shows the 13C NMR spectra of 4-MET in 70 vol% ethanol solutions and the 13C NMR peak assignments. When the ethanol solution with 4-MET was aged for seven weeks, a new NMR peak "11", assigned to methyl carbon of ethyl ester, appeared at 13.67 ppm in the lower 13C NMR spectrum. The appearance of this peak was due to the esterification of 1- or 2-carboxylic acid in 4-MET by ethanol.

Figure 2 shows the expanded 13C NMR spectra of the carbonyl and methylene regions of 4-MET in 70 vol% ethanol solutions under different aging periods. In the 13C NMR spectra of the carbonyl region, new NMR peaks "9" and "circle 8", assigned to the ester carbonyl carbons in which 1- or 2-carboxylic acid in 4-MET were esterified by ethanol, were detected at 168.84 and 167.87 ppm respectively. Reflecting the esterification reaction, an NMR peak

![Diagram](Image)

Fig. 1 13C NMR spectra of 4-MET in 70 vol% ethanol solution and 13C NMR peak assignments. Upper spectrum is 4-MET with an aging period of 0 days. Lower spectrum is for aging period of 7 weeks. There, NMR peaks "11" and "2*" were assigned to the methylene carbon and methyl carbon of ethanol, respectively.
"7", attributed to the benzyl ester carbonyl carbons in 4-MET, split into two distinct NMR peaks, identified as "7'" and "circle 7" peaks respectively. As the aging period was extended, the intensities of both NMR peaks increased. Furthermore, new NMR peaks appeared — namely "g" and "g'" attributed to the carbonyl carbons in 4-carboxylic acid in non-esterified and esterified trimellitic acid, as well as NMR peak "d" attributed to ester carbonyl carbon in HEMA.

In addition, two split NMR peaks "10", attributed to the methylene carbons in ethyl ester, were detected at 62.74 and 62.85 ppm in the methylene region. Appearance of these peaks was due to the esterification reaction of 1- or 2-carboxylic acid in 4-MET. Furthermore, NMR peaks "e" and "f", assigned to 1- and 2-methylene carbons in HEMA, and NMR peak "β" assigned to the methylene carbons in EG, appeared at 60.20, 67.60, and 63.46 ppm, respectively. These findings demonstrated that the benzyl ester portion in esterified and non-esterified 4-MET had hydrolyzed, and that the methacryloxy ester portion in HEMA, produced from the hydrolysis of benzyl ester portion, had also become hydrolyzed. Then, apart from the assigned peaks, unassigned small NMR peaks were detected at 66.71 ppm.

Conversely, when 70% methanol solution with 4-MET was aged for seven weeks, the new split NMR peaks of "10", assigned to the methyl carbons of methyl ester in which 1- or 2-carboxylic acid in 4-MET was esterified by methanol, appeared at 53.19 and 53.29 ppm, as shown in the lower $^{13}$C NMR spectrum in Fig. 3. Reflecting an esterification reaction, new NMR peaks "g'" and "circle 8", assigned to the ester carbonyl carbons where 1- or 2-carboxylic acid in 4-MET had been esterified by methanol, were detected at 169.60 and 168.53 ppm, respectively, as shown in the $^{13}$C NMR spectrum of the carbonyl region in Fig. 4. The NMR peak "7", assigned to the benzyl ester carbonyl carbons in 4-MET, split into two distinct NMR peaks and were identified as peak "7'" and peak "circle 7".

By extending the aging period, the intensities of both "7'" and "circle 7" peaks increased. Furthermore, new NMR peaks appeared — namely "g" and "g'" attributed to the carbonyl carbons in 4-carboxylic acid of non-esterified and esterified trimellitic acid, as well as NMR peak "d" attributed to ester carbonyl carbon in HEMA. In addition, NMR peaks "e" and
Fig. 3 $^{13}$C NMR spectra of 4-MET in 70 vol% methanol solution and $^{13}$C NMR peak assignments. Upper spectrum is 4-MET with an aging period of 0 days. Lower spectrum is for aging period of 7 weeks. There, NMR peak "1" was assigned to the methyl carbon of methanol.

Fig. 4 Expanded $^{13}$C NMR spectra of carbonyl and methylene regions of 4-MET in 70 vol% methanol solution under different aging periods. Upper spectrum is 4-MET with an aging period of 0 days. Middle spectrum is for aging period of 7 weeks. Lower spectrum is for aging period of 14 weeks.
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Fig. 5 $^{13}$C NMR spectra of 4-MET in 70 vol% acetone solution and $^{13}$C NMR peak assignments. Upper spectrum is 4-MET with an aging period of 0 days. Lower spectrum is for aging period of 7 weeks. There, NMR peak "1s" was assigned to the methyl carbon of acetone.

Fig. 6 Expanded $^{13}$C NMR spectra of carbonyl and methylene regions of 4-MET in 70 vol% acetone under different aging periods. Upper spectrum is 4-MET with an aging period of 0 days. Middle spectrum is for aging period of 7 weeks. Lower spectrum is for aging period of 14 weeks.
“5”, attributed to both 1- and 2-methylene carbons in HEMA, and NMR peak “6” attributed to the methylene carbons in EG, were detected at 60.30, 67.85, and 63.61 ppm, respectively, as shown in the methylene region in Fig. 4. Apart from the assigned peaks, an unassigned NMR peak was detected at 66.89 ppm.

**Altered degradation mechanism of 4-MET in acetone solution**

Figure 5 shows the $^{13}$C NMR spectra of 4-MET in 70 vol% acetone solutions and the $^{13}$C NMR peak assignments. Furthermore, the expanded $^{13}$C NMR spectra of the carbonyl and methylene regions of 4-MET in acetone, under different aging periods, are shown in Fig. 6.

As the aging period of 4-MET in acetone solution was extended, new NMR peaks “g”, “h”, “i”, and “d”, attributed to the carbonyl carbons of 4-, 2-, and 1-carboxylic acids in trimellitic acid, as well as of methacryloxy ester carbonyl carbon in HEMA, appeared respectively in the $^{13}$C NMR spectra of the carbonyl region. Appearance of these peaks was due to the hydrolysis of benzoyl ester portion in 4-MET. Furthermore, NMR peaks “e” and “f”, attributed to both 1- and 2-methylene carbons in HEMA, were detected in the $^{13}$C NMR spectra of the methylene region. Apart from the assigned peaks, an unassigned NMR peak was detected at 66.89 ppm.

**DISCUSSION**

In this study, we examined the effects arising from the different types of solvent used on the degradation of 4-MET by means of an accelerated aging test using the $^{13}$C NMR technique.

To understand the degradation mechanism of 4-MET in 70 vol% solvated solutions, we focused on the following NMR peaks: “7” assigned to benzoyl carbonyl carbon and “5 & 6” assigned to 1- and 2-methylene carbons in 4-MET. These peaks were of special interest in this study because NMR peaks “7” and “5 & 6” shifted and split into several distinct peaks. This splitting reflected changes in the environment where 4-MET had existed, and thereby reflected the

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**Fig. 7** Relative intensities of NMR peaks “7”, “7’ circle 7”, and “g & g’” as a function of the aging period when 70 vol% ethanol or methanol solution with 4-MET, was aged. NMR peak “7” was assigned to benzoyl ester carbonyl carbon in 4-MET. NMR peaks “7’ & circle 7” were assigned to benzoyl ester carbonyl carbons in esterified 4-MET of which the 1- or 2-carboxylic acid was esterified. NMR peaks “g & g’” were assigned to carbonyl carbons of 4-carboxylic acid in non-esterified and esterified trimellitic acid.

Solvated solution: 70 vol% ethanol solution

●: NMR peak “7”; ▲: NMR peaks “7’ & circle 7”;
■: NMR peaks “g & g’”

Solvated solution: 70 vol% methanol solution

○: NMR peak “7”; △: NMR peaks “7’ & circle 7”;
□: NMR peaks “g & g’”

**Fig. 8** Relative intensities of NMR peaks “5 & 6, 5’ & 6’, circles 5 & 6’, “e & f’, and “□” as a function of the aging period when 70 vol% ethanol or methanol solution containing 4-MET was aged. NMR peaks “5 & 6, 5’ & 6’, circles 5 & 6’” were assigned to 1- and 2-methylene carbons in non-esterified and esterified 4-MET. NMR peaks “e & f’” were assigned to 2- and 1-methylene carbons in HEMA. NMR peak “□” was assigned to both methylene carbons in ethylene glycol.

Solvated solution: 70 vol% ethanol solution

●: NMR peaks “5 & 6, 5’ & 6’, circles 5 & 6’; ▲: NMR peaks “e & f’;■: NMR peak “□”

Solvated solution: 70 vol% methanol solution

○: NMR peaks “5 & 6, 5’ & 6’, circles 5 & 6’; △: NMR peaks “e & f’; □: NMR peak “□”

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Chemical structures of the subproducts produced by the hydrolysis of the ester portion in 4-MET. We then determined the relative intensities of NMR peaks "7", "7'" & circle "7", "g & g'" as shown in Fig. 7, as well as those of "5 & 6, 5' & 6', circles 5 & 6", "e & f", and "β" in Fig. 8.

When alcohol was used as a solvent for 4-MET, the esterification of 1- or 2-carboxylic acid in 4-MET by alcohol occurred during the initial stages of 4-MET degradation. Rate of esterification reaction was strongly dependent on the type of alcohol used. Esterification rate by methanol was faster than the rate observed for ethanol, largely because the molecular volume and steric hindrance of methanol were smaller than those of ethanol. When the solution's aging period was extended to 14 weeks, 4-MET that remained in the solution became 9% for 70% methanol solution and 23% for 70% ethanol solution (Fig. 7). This result was due to the esterification reaction of 1- or 2-carboxylic acid in 4-MET by methanol or ethanol and the hydrolysis reaction of benzoyl ester portion in 4-MET.

Besides, HEMA and trimellitic acid subproducts were produced. The amount of trimellitic acid produced was 20% for methanol solution and 8% for ethanol solution. The esterification of 4-MET by methanol appeared to accelerate the hydrolysis of benzoyl ester portion in 4-MET. Consequently, methacrylic acid and ethylene glycol were produced due to the hydrolysis of methacryloxy ester portion in the produced HEMA. The amount of EG produced in the methanol solution was greater than that in the ethanol solution, as shown in Fig. 8.

Conversely, when 4-MET was solvated in 70% acetone solution, the benzoyl ester portion in 4-MET became hydrolyzed. Similarly, the methacryloxy ester portion in HEMA was also hydrolyzed, as shown in Fig. 9. When 4-MET was aged for 14 weeks, approximately 14% of 4-MET was hydrolyzed. In addition, HEMA and trimellitic acid subproducts were pro-

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Fig. 9 Relative intensities of NMR peaks "7", "7'" & circle "7", and "g & g'" as a function of the aging period when 70 vol% acetone or ethanol solution containing 4-MET was aged. NMR peak "7" was assigned to benzoyl ester carbonyl carbon in 4-MET. NMR peaks "7'" & circle "7" were assigned to benzoyl ester carbonyl carbons in esterified 4-MET of which the 1- or 2-carboxylic acid was esterified. NMR peaks "g & g'" were assigned to carbonyl carbons of 4-carboxylic acid in non-esterified and esterified trimellitic acid.

Solvated solution: 70 vol% acetone solution
○: NMR peak "7"; △: NMR peaks "7'" & circle "7";
□: NMR peaks "g & g'"

Solvated solution: 70 vol% ethanol solution
○: NMR peak "7"; △: NMR peaks "7'" & circle "7";
□: NMR peaks "g & g'"

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Fig. 10 Relative intensities of NMR peaks "5 & 6, 5' & 6', circles 5 & 6", "e & f", and "D" as a function of the storage period when 70 vol% acetone or ethanol solution containing 4-MET was aged. NMR peaks "5 & 6, 5' & 6'", and circles 5 & 6" were assigned to 1- and 2-methylene carbons in non-esterified and esterified 4-MET. NMR peaks "e & f" were assigned to 2- and 1-methylene carbons in HEMA. NMR peak "D" was assigned to both methylene carbons in ethylene glycol.

Solvated solution: 70 vol% acetone solution
○: NMR peaks "5 & 6, 5' & 6'", circles 5 & 6";
△: NMR peaks "e & f"; □: NMR peak "D"

Solvated solution: 70 vol% ethanol solution
○: NMR peaks "5 & 6, 5' & 6'", circles 5 & 6";
△: NMR peaks "e & f"; □: NMR peak "D"
duced. The amount of hydrolyzed 4-MET in the acetone solution was greater than that observed in the ethanol solution, as shown in Fig. 10.

By means of transmission electron microscopy, Nishiyama et al. investigated the effects of aging of UB on the ultrastructure of the hybrid layer created at the resin-dentin interface. Aging of UB resulted in an increase in hybrid layer thickness as well as changes in the layer's ultrastructure. In this study, two key factors have been identified to affect the formation, ultrastructure, and quality of the hybrid layer: degradation caused by the esterification reaction with alcohol, as well as the hydrolysis reaction of 4-MET. Specifically, EG and TA produced as sub-products might reduce the long-term bonding stability of resin to teeth, since the quality of hybrid layers that contain EG and TA should decrease.

Furthermore, we detected unassigned small NMR peaks at approximately 67 ppm in the 13C NMR spectra of the methylene region, as shown in Figs. 2, 4, and 6. Most probably, this NMR peak could be assigned to the 1-methylene carbon in 4-(2-hydroxyethyl)trimellitic acid. Appearance of this NMR peak, assigned to 1-methylene carbon in 4-(2-hydroxyethyl)trimellitic acid, demonstrated that the hydrolysis of methacryloxy ester portion in 4-MET also occurred as a sub-reaction during the initial stages of the degradation.

Based on the NMR analysis results obtained in this study, the degradation mechanism of 4-MET differed between the alcohol and acetone solutions. When 4-MET was solvated in the alcohol solution, the etching potential of the self-etching primers and one-step bonding agents containing 4-MET should decrease, since the carboxylic acid in 4-MET was esterified. In contrast, when acetone was used as a solvent, the etching efficacy remained unchanged since the esterification reaction of 4-MET did not occur. However, the benzoyl ester portion in 4-MET and the methacryloxy ester portion in the produced HEMA eventually became hydrolyzed. As a result of the hydrolysis of both ester portions in 4-MET, ethylene glycol and trimellitic acid were produced. The production of EG and TA might then lead to decreased bond strength and bonding durability of resin to the tooth, chiefly because of the deterioration in the quality of the created hybrid layer.

CONCLUSIONS

4-MET, commonly utilized in solvated self-etching primers and one-step bonding agents, becomes altered and degraded upon use. In this study, it was found that degradation mechanism was strongly dependent on the type of solvent used. When an alcohol-based solution was used for 4-MET, the esterification of 1- or 2-carboxylic acid in 4-MET occurred. As a result, the etching efficacy of 4-MET on tooth components would decrease. Conversely, when acetone was used as the solvent, the etching efficacy of 4-MET did not change since esterification of the carboxylic acid in 4-MET by acetone did not occur.

However, when the aging period of 4-MET solvated solutions was prolonged, hydrolysis of the benzoyl ester portion in non-esterified and esterified 4-MET occurred. In addition, the methacryloxy ester portion in the produced HEMA also became hydrolyzed. Consequently, methacrylic acid, non-esterified and esterified trimellitic acid, and ethylene glycol were also produced as subproducts. In particular, trimellitic acid and ethylene glycol produced would most likely affect the bonding performance and durability of the resin to the tooth components, by virtue of the inferior quality of the hybrid layer created by self-etching primers or one-step bonding agents containing the altered 4-MET.

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