

Studies on Adhesive Monomers for Teeth. V. Influence of Substituents in Methacrylamide Derivatives

SHINYA KITOH and MIKIO MIYAKE, *Applied Research Laboratories, Lion Corporation, Tajima, Odawara-shi, Kanagawa, Japan*,
SATOSHI HAYASHI, *Development Laboratories, Lion Corporation, Honjo, Sumida-ku, Tokyo, Japan*, and KEISUKE KURITA, *Department of Industrial Chemistry, Faculty of Engineering, Seikei University, Musashino-shi, Tokyo, Japan*

Synopsis

In order to shed light on the relationship of monomer structure and adhesiveness to tooth enamel, methacrylamides having various substituents were synthesized and evaluated as dental adhesives. Among 17 methacrylamides synthesized here, those having *N-m*- and *N-p*-carbethoxyphenyl, *N-p*-fluorophenyl, and *N*-3-carboxycyclohexyl groups showed adhesive tensile strength of more than 100 kg/cm² with minimal drops in strength on standing, indicating high potentials as novel adhesives. It was also confirmed that a carboxyl group enhances adhesive tensile strength peculiarly regardless of skeletal structures.

INTRODUCTION

The need of good adhesives with high adhesive tensile strength, low extents of decrease in the strength on standing, and also high biocompatibility has been more and more pronounced recently in dentistry. It has been suggested that good adhesion is achieved with monomers containing both hydrophilic and hydrophobic groups in a proper balance.¹ Among such monomers with high tensile strength, 4-methacryloyloxyethyltrimellitic acid² and 2-methacryloyloxyethyl hydrogenphosphate³ synthesized by Nakabayashi et al. and *N*-(2-hydroxy-3-methacryloyloxypropyl)-*m*-aminobenzoic acid,⁴ were prepared are typical examples. The effectiveness of these monomers may at least in part be interpreted in terms of their structural feature that the sites of polymerization and those interacting with tooth enamel are apart at considerable distances.

In our continuing study to develop high performance dental adhesives focused on the effects of monomer structures on adhesion,⁴⁻⁷ we previously evaluated some methacrylamide derivatives,⁶ which are expected to be more resistive against hydrolysis than ester moieties under the conditions for practical use as dental adhesives. As a result, methacrylamides were found to show remarkable adhesiveness when they have carboxyl and phenyl groups, although they are smaller molecules compared to those mentioned above. This prompted us to further explore the high potential of methacrylamide derivatives having different *N*-substituents, especially those with some hydrophobic groups including various kinds of phenyls, cyclohexyls, and pyridyls. This

TABLE I
Preparation of the Primer

	Composition A (%)	Composition B (%)
Methyl methacrylate	82.0	82.6
Poly(methyl methacrylate)	16.4	16.5
Dimethyl- <i>p</i> -toluidine	1.6	—
Benzoyl peroxide	—	0.9

paper describes the influence of *N*-substituents of such methacrylamides on the adhesiveness to tooth enamel in comparison with those of the corresponding glycidyl methacrylate derivatives reported previously.⁴

EXPERIMENTAL

Syntheses of *N*-Substituted Methacrylamides

Monomers were synthesized by the condensation reaction involving methacryloyl chloride and substituted anilines or some other amines in benzene in the presence of triethylamine as the acid acceptor. Reaction products were generally purified by recrystallization, but two monomers were purified by column chromatography.

Evaluation of Adhesiveness

Bonding Agent. A 5% w/w monomer solution in ethanol was used for evaluation of adhesiveness to tooth enamel.

Preparation of the Primer. The compositions A and B shown in Table I were mixed to form the primer just before use.

Preparation of Adherent Specimens. A consistent surface of bovine enamel for adhesion tests was obtained by grinding with an optical emery powder of up to no. 1200. A poly(methyl methacrylate) (PMMA) rod of 6 mm in diameter was polished in the same way.

Adhesion Test. A polished bovine enamel specimen was etched with 3*M* aqueous H₃PO₄ solution for 30 s and washed with water for 30 min. The

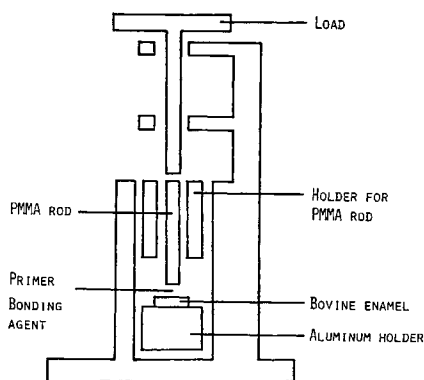


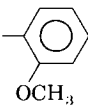
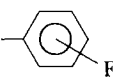
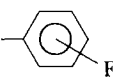
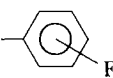



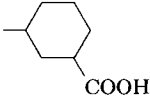
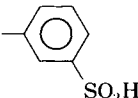
Fig. 1. Adhesive apparatus.

specimen dried compressed air was installed in the apparatus shown in Figure 1. A bonding agent was applied to the etched enamel surface, which was dried similarly. The surface was then coated with the primer mixture. A PMMA rod was set perpendicular to the enamel surface with a 500 g weight. The adhered specimen was allowed to stand for 30 min at room temperature and then immersed in Greenwood's artificial saliva⁸ at 37°C. The adhesive tensile strength was measured after 2 weeks and 2 months with an autograph (Toyo Seiki Mfg., Tokyo, Japan) at a crosshead speed of 5 mm/min. The average value and standard deviation were calculated from the measured values for five specimens.

RESULTS AND DISCUSSION

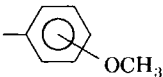
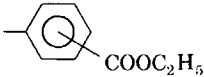
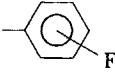
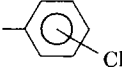



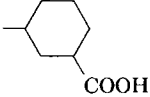
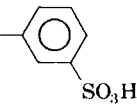
All the monomers synthesized by the condensation reaction of methacryloyl chloride and substituted anilines and some other amines were identified by IR and NMR spectroscopies, and/or elemental analyses. The results are summarized in Table II. The yield values varied over a wide range after purification,

TABLE II
Syntheses of Some New Methacrylamide Derivatives

$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2=\text{C}-\text{CONH}-\text{R} \\ \text{R} \end{array}$	Yield (%)	mp (°C)
	37	— ^a
	<i>o</i> - 10	43-44
	<i>m</i> - 12	72-73
	<i>p</i> - 16	74-77
	18	76-77
	29	130-132
	20	113-114
	11	141-143
	5	— ^a

^aSeparated by column chromatography on silica gel.

TABLE III
 Adhesive Tensile Strength of *N*-Substituted Methacrylamides between
 Bovine Enamel and Poly(methyl Methacrylate)

$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2=\text{C}-\text{CONH}-\text{R} \end{array}$	Tensile strength (kg/cm ²)		
	2 weeks	2 months	
	<i>o</i> -	95 ± 10	63 ± 26
	<i>m</i> -	93 ± 26	82 ± 28
	<i>p</i> -	91 ± 4	104 ± 36
	<i>o</i> -	67 ± 22	56 ± 30
	<i>m</i> -	139 ± 49	116 ± 44
	<i>p</i> -	104 ± 28	86 ± 30
	<i>o</i> -	69 ± 29	29 ± 10
	<i>m</i> -	47 ± 8	85 ± 25
	<i>p</i> -	117 ± 52	84 ± 26
	<i>o</i> -	74 ± 46	28 ± 17
	<i>m</i> -	45 ± 13	86 ± 24
	<i>p</i> -	85 ± 36	93 ± 31
		81 ± 45	92 ± 23
		77 ± 22	48 ± 15
		67 ± 15	56 ± 34
		119 ± 42	113 ± 24
		44 ± 27	37 ± 17
Control		50 ± 23	39 ± 25

but no effort was made to optimize the reaction and recrystallization conditions.

The monomers prepared here were then subjected to adhesion test using PMMA rods and bovine enamel. Adhesive tensile strength measured after 2 weeks and 2 months were indicated in Table III. *N-m*- and *N-p*-carbethoxyphenylmethacrylamide, *N-p*-fluorophenylmethacrylamide, and *N-3*-carbox-

N-cyclohexylmethacrylamide showed more than 100 kg/cm² of tensile strength at a period of 2 weeks and only slight drops in the strength on standing. Tensile strength values of *N*-*p*-methoxyphenylmethacrylamide, *N*-*p*-chlorophenylmethacrylamide, and *N*-3-pyridylmethacrylamide were 80–90 kg/cm² initially, but they increased to over 90 kg/cm² on standing for 2 months. These six kinds of monomers are considered to be qualified for practical use as tooth adhesives.

Among the substituents, the methoxy group on the phenyl ring showed little position specificity in terms of tensile strength as in the case of the corresponding glycidyl methacrylate derivatives, 2-hydroxy-3-methoxyphenylaminopropylmethacrylates.⁴ The values for methoxyphenylmethacrylamides, however, were around 90 kg/cm², which were approximately double those of the structurally related methacrylate derivatives.

As for the carbethoxy group on the phenyl ring, its bonding position greatly affected the tensile strength of the methacrylamides, although in the corresponding glycidyl methacrylate series,⁴ the strength was little influenced by the bonding position of the substituent. A distinct dependency of the strength on the position of the carbethoxy group is evident in Table III, and the order was *m*-> *p*-> *o*-. Particularly, the meta isomer showed the highest initial tensile strength among the monomers prepared in this study. In these methacrylamide derivatives, a polymerization site of the monomer molecule is not far apart from the site presumed to be concerned with adhesion, and consequently the adhesiveness would be influenced more sensitive by the difference in the position of a substituent than that of the glycidyl methacrylate derivatives.

There was observed very similar substituent effects for two series of halogenated monomers: one containing a fluoro group and the other, a chloro group. The tensile strength was in the *p*-> *o*-> *m*-isomer order for both series. The *p*-isomers had high strength even after 2 months, but the *o*-isomers recorded marked reduction on standing. The *m*-isomers, although their initial strength was low, were characterized by remarkable increase in strength on standing for 2 months.

Instead of a benzene ring, a pyridine ring was also incorporated as an aromatic ring having appreciable hydrophilicity and basicity. Two pyridine-containing monomers, *N*-3-pyridylmethacrylamide and *N*-4-pyridylmethacrylamide, were found to show fairly good initial adhesiveness of around 80 kg/cm², but the latter monomer was inferior owing to a drop in tensile strength on standing.

N-cyclohexylmethacrylamide, a monomer having a hydrophobic aliphatic ring, showed only slightly higher tensile strength than a control, which is in good accord with our previous deduction^{4,5,7} from the results of monomers having bulky aliphatic groups. Substitution of a carboxyl group on the cyclohexyl ring could, however, improve the poor tensile strength remarkably to 119 kg/cm², and the effectiveness of a carboxyl group substitution was confirmed as in *N*-phenylmethacrylamide derivative series.⁶ The efficiency of a carboxyl group suggested the incorporation of a sulfonic acid group which, as well as a carboxyl group, is assumed to have a high possibility of chemical interaction with enamel surface. A monomer having a sulfonic acid group on a phenyl ring, however, showed a tensile strength of only 44 kg/cm² counter to

our expectation, and the sulfonic acid group turned out to be unsuitable for tooth adhesive. This becomes especially evident when compared with the result (136 kg/cm^2)⁶ for the corresponding monomer having a carboxyl group at the same position, *N-m*-carboxyphenylmethacrylamide. *N*-carboxymethyl-*N'*-methacryloylpiperazine⁹ is also a monomer with high tensile strength. These results indicate that a carboxyl group has a peculiar tendency to improve the adhesiveness independent of the structure of hydrophobic groups in monomers.

Consequently, among monomers we prepared here, methacrylamides containing *N-m*- and *N-p*-carbethoxyphenyl, *N-p*-fluorophenyl, and *N*-3-carboxycyclohexyl groups were found to exhibit high initial tensile strength above 100 kg/cm^2 and only a slight decrease on standing. Though initial strength was below 100 kg/cm^2 , strength after 2 months was above 90 kg/cm^2 for those containing *N-p*-methoxyphenyl, *N-p*-chlorophenyl, and *N*-3-pyridyl groups. These monomers thus proved to be useful adhesives for tooth with high potentials. Among some substituent groups, a carboxyl group was confirmed to be most appropriate to promote adhesiveness for a wide variety of skeletal structures, whereas a sulfonic acid group was unsuitable.

References

1. N. Nakabayashi, *Nippon Fukugozairyo Gakkai-shi*, **4**, 135 (1978).
2. M. Takeyama, N. Nakabayashi, N. Kayabuchi, and E. Masuhara, *J. Jpn. Soc. Dent. Appar.*, **19**, 179 (1978).
3. J. Yamauchi, E. Masuhara, N. Nakabayashi, K. Shibuya, and T. Wada, *Jpn. Pat. Kokai* 53-110637 (1978) (to Kuray Co., Ltd.).
4. S. Kitoh, M. Miyake, S. Hayashi, and K. Kurita, *Kobunshi Ronbunshu*, **39**, 319 (1982).
5. S. Kitoh, M. Miyake, S. Hayashi, and K. Kurita, *Kobunshi Ronbunshu*, **39**, 817 (1982).
6. S. Kitoh, M. Miyake, S. Hayashi, and K. Kurita, *Kobunshi Ronbunshu*, **40**, 411 (1983).
7. S. Kitoh, M. Miyake, S. Hayashi, and K. Kurita, *Kobunshi Ronbunshu*, **40**, 575 (1983).
8. T. Kanetake, *Dental Apparatus and Materials*, Ishiyaku, Tokyo, 1971, p. 41.
9. E. Masuhara, K. Kojima, J. Tarumi, and H. Hotta, *Rep. Res. Inst. Med. Mater. Tokyo Med. Dent. Univ.*, **1**, 29 (1967).

Received January 4, 1986

Accepted May 5, 1986