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What is This?
The Effect of Catalyst Structure on the Synthesis of a Dental Restorative Monomer

M. FARAHANI, A.D. JOHNSTON, and R.L. BOWEN

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The addition product of 2-hydroxyethyl methacrylate (HEMA) and pyromellitic dianhydride (PMDA), known as PMDM, is a mixture of two structural isomers. The para PMDM isomer—currently used in mediating adhesive bonding of restorative materials to hard tooth tissues—is a crystalline solid. The meta isomer is a liquid. In the synthesis of PMDM, the para isomer, which can be purified by crystallization, is usually present to the extent of only 50% of the product mixture. The effect of the amine catalyst structure was studied relative to its role in increasing the yield of the para isomer, either by a reduction in the amount of the meta isomer or by an increase in the extent of overall reaction. The chemical structure of the amine catalyst had an important role in the synthesis of PMDM and influenced the ratio of the isomers. Among aliphatic amines, especially noteworthy as catalysts that gave excellent yields of the para isomer in high purity were N,N-di-isopropyl-ethylamine and hexamethylenetetramine.


Introduction.

A three-step protocol for adhesive bonding of dental resins to dentin and enamel was previously developed (Bowen et al., 1982). The first step was the application of a mordant solution of acidic, aqueous, metallic oxalate to the surface to remove the smeared (disturbed) layer resulting from instrumental techniques used to remove carious material. The second step was the application of an acetone solution of an N-substituted amino acid, NPG-GMA (the addition product of N-phenylglycine (NPG) and glycidyl methacrylate) or NTG-GMA (the addition product of N-tolylglycine and glycidyl methacrylate). The third step was the application of an acetone solution of PMDM (the addition product of two moles of 2-hydroxyethyl methacrylate (HEMA) per mole of pyromellitic dianhydride (PMDA; 1,2,4,5-benzene tetracarboxylic dianhydride)).

Subsequent work showed that the three-step protocol could be reduced to a two-step procedure (Bowen et al., 1987) by combining NPG with dilute nitric acid as the first step. NPG in place of its adduct with glycidyl methacrylate is effective in either protocol (Bowen, 1985). The second step currently remains the application of a PMDM solution to the tooth surface immediately prior to placement of the dental resin or composite.

In the synthesis of PMDM, the reaction product consists of a mixture of para and meta regio-isomers, shown in Fig. 1 (Johnston and Bowen, 1987). Because of the extensive use of these monomers, improvements in synthetic procedures were investigated.

The overall purpose of this study was to assess the effect of the catalyst structure on the reactivity of the HEMA with the anhydride linkages of PMDA and the para/meta isomer ratio of the products. At present, the para isomer is used most extensively because it is a crystalline solid that is readily purified by re-crystallization. Efforts to crystallize the meta isomer have not been successful. This study was therefore aimed at producing a higher yield of the para PMDM monomer. The theoretical yield of the para isomer from the addition reaction is 50%. It was of interest to determine whether the para/meta isomer ratio could be altered in favor of one or the other isomer by changing the structure and basicity of the catalytic amine. Control of the isomer ratio would allow more efficient production of either isomer, assist industry in the current use of the para isomer, and permit planned studies of the comparative effectiveness of the two isomers in adhesives and other applications.

Materials and methods.

The organic chemicals used in these experiments were all purchased from Aldrich Chemical Co. (P.O. Box 355, Milwaukee, WI 53201). The 1,2,4,5-benzene tetracarboxylic dianhydride (PMDA, 97%) was freshly sublimed before each reaction (175°C, 26.7 Pa). The 2-hydroxyethyl methacrylate (HEMA, 97%) was stored in a refrigerator over molecular...
sieves (4Å) to maintain a minimal water content. The 2,6-di-tert-butyl-4-methylphenol (BHT, 99 + % Gold Label) was used directly from the bottle as a polymerization inhibitor. The amines listed in the Table were used directly as received.

The proton magnetic resonance (1H NMR) spectra of the isomeric PMDM mixtures were recorded with a JEOL GSX 270 MHz FT NMR spectrometer with deuterated acetone as solvent and 0.3% tetramethylsilane (TMS) as internal standard. Electronic integration of the spectra yielded the para/meta isomer product ratios and the extent of conversion.

The standard conditions of PMDM synthesis were the following: The reaction vessel was a 1000-mL, single-neck, round-bottom flask equipped with a drying-tube-capped condenser, magnetic stirring bar, heating mantle, and magnetic stirring motor. The materials were added in the following order: PMDA, 0.10 mole; HEMA, 0.22 mole; BHT (2,6-di-tert-butyl-4-methylphenol), 0.001 mole; THF (tetrahydrofuran), 100 mL; and the amine catalysts listed in the Table, 0.02 mole. The solid PMDA went into solution slowly as the flask was heated. The solution was refluxed for one h; then the reaction mixture was assayed by 1H NMR analysis (Fig. 2). After being cooled, the reaction mixture was diluted with diethyl ether (500 mL). Any PMDA that had been hydrolyzed to give the tetra-acid was insoluble in the reaction mixture and was removed by vacuum filtration through a pad of celite on sand on a coarse-fritted glass filter. The organic solution was transferred to a

<table>
<thead>
<tr>
<th>Table</th>
<th>EFFECTS OF AMINE CATALYSTS ON REACTION PRODUCTS IN THE SYNTHESIS OF PMDM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amine</strong></td>
<td><strong>pKa</strong></td>
</tr>
<tr>
<td><strong>ALIPHATIC:</strong></td>
<td></td>
</tr>
<tr>
<td>N,N-diisopropyl-ethyamine</td>
<td>11.1</td>
</tr>
<tr>
<td>Hexamethylene-tetramine</td>
<td>6.3</td>
</tr>
<tr>
<td>1,4-Diazabicyclo-[2.2.2]-octane</td>
<td>8.2</td>
</tr>
<tr>
<td>Triethylamine</td>
<td>10.8</td>
</tr>
<tr>
<td>Tripropylamine</td>
<td>10.7</td>
</tr>
<tr>
<td>Tributylamine</td>
<td>9.9</td>
</tr>
<tr>
<td><strong>BENZYLIC:</strong></td>
<td></td>
</tr>
<tr>
<td>N,N-dimethyl-benzylamine</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>AROMATIC:</strong></td>
<td></td>
</tr>
<tr>
<td>N,N,N’,N’-tetramethyl-1,4-phenylenediamine</td>
<td>10.1</td>
</tr>
<tr>
<td>Pyridine</td>
<td>5.4</td>
</tr>
<tr>
<td>N,N-dimethyl-aniline</td>
<td>5.2</td>
</tr>
</tbody>
</table>

The PMDM syntheses accomplished as part of this study are summarized here. Each amine is listed with the data pertaining to that amine. The pKa, a reference for the pKa measurement, are in the first two columns after the amine. The para/meta mono-addition product ratio is next. If there was no mono-addition product (Fig. 6) observed in the reaction, then there are only two values in the ratio. The ‘Dried’ Crude Mass column listed the percent yield recovered after work-up and 48-hour drying under an air stream. The final ratio reflects the integrations of the triply re-crystallized PMDM mixture, and the next column discloses the melting point of the sample. The yield values are in percent and the grams of material collected after the reaction. Each reaction that produced the product was repeated at least once and usually twice.

(a) Hall (1957) and Hull et al. (1969), (b) Perrin (1965), (c) Dean (1979), (d) Kudryavtseva et al. (1980), (e) Morrison and Boyd (1973), and (f) Arnet et al. (1970).

*The yield of para PMDM is based on the weight recovered after the third re-crystallization divided by the amount of para PMDM in the crude mixture, determined by the starting quantity of PMDA and the NMR ratios of the pyromellitic reaction products.

† Some product spilled before being weighed; mass recovered is presented in the Table, but yield percentage is unknown.

Note: The tribenzylamine was difficult to remove from the reaction mixture; therefore, the 35% and 8.6 g yield is after only two crystallizations. The "‘dried’ crude weight" represents the % yield of the original reaction product mixture after being washed and dried. Amounts over 100% probably represent incomplete removal of solvents, catalyst, HEMA, etc., and amounts under 100% could represent incomplete reactions and/or losses during washing.

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1000-mL separatory funnel for successive washes with 1 mol/L aqueous HCl (3 × 150 mL), water (3 × 150 mL), and saturated aqueous sodium chloride (3 × 150 mL). The remaining organic materials were poured into a large beaker (2000 mL) and were concentrated by evaporation of the solvents under a dry air stream. After 48 h, the crude solid was again assayed by 1H NMR, dissolved completely in methanol (130 mL), and warmed to 65°C. After drop-wise addition of water caused the solution to become cloudy, the mixture was allowed to cool overnight at room temperature. The crude crystals were filtered, subjected to 1H NMR analysis, and re-crystallized from methanol/water mixtures two more times. After the third re-crystallization, the final 1H NMR (Fig. 3) was recorded, and the para/meta isomer ratio was determined (Table).

Results.

The para-PMDM isomer was a shiny, white crystalline material with a melting-point range of 161-162°C. The melting-point-range data for the PMDM products are listed in the Table. A lower and wider melting-point range corresponded to a less pure para PMDM sample.

The addition of the hydroxyl group of HEMA across the anhydride linkages of PMDA did not occur within one h unless a catalytic amount of tertiary amine was present. Ten mole percent of amine was used, based on the HEMA, with lower amine concentration giving an inadequate reaction rate under these conditions. Twelve tertiary amines were tested (Fig. 4). Six of these bases were aliphatic (pKa's 6.3 to 11.1), two were benzyl amines (pKa's 7.4 and 8.9), and four were aromatic (pKa's about 9 - 10.1).

The amines in the Table are classified as aliphatic, benzylic, or aromatic amines, listed in descending order of purity (highest m.p.) and yield of para PMDM. The percent yield of para PMDM for each amine listed in the Table was calculated from the para isomer component in the crude product (based on a normalized ratio determined by 1H NMR analysis) and that collected after the third re-crystallization.

The 1H NMR spectra were clearly diagnostic for the isomers. The para isomer, 1,4-di[2-(2-methyl-2-propenoate)ethyl]phthalate-2,5-dicarboxylic acid, had one resonance (8 8.15 ppm) for the two magnetically equivalent hydrogen atoms of the central aromatic ring (Fig. 3). The meta isomer, 1,3-di[2-(2-methyl-2-propenoate)ethyl]phthalate-4,6-dicarboxylic acid, was not as rotationally symmetrical and had two singlets corresponding to the two non-equivalent aromatic hydrogen atoms. These resonated upfield (8 8.0 ppm) and downfield (8 8.30 ppm) with respect to the aromatic signal in the desired para PMDM isomer, as shown in Fig. 2.

Discussion.

The data in the Table show the yields of para PMDM as determined by the characteristics of the amines evaluated. The electron density of the nitrogen controls electron donation, indicated by pKa, higher values implying basicity and nitrogen's tendency to accept a proton. Steric hindrance from physical bulk of substituents around the nitrogen atom restricts the possible arrangements of the reactants in the transition state. Solubility and other characteristics influence ease of separation during the purification steps.

The mechanism shown in Fig. 5 depicts the role of the amine in the reaction of alcohols such as HEMA and anhydrides such as PMDA (March, 1977; Butler and Gold, 1961; Fersht and Jencks, 1970a, b). The amine reacts with the anhydride to yield a zwitterionic intermediate (I). The positively charged N-trisubstituted amide in structure I provides an excellent leaving group for displacement by the nucleophilic oxygen of the HEMA. This displacement of the amine by the alcohol results in the zwitterionic protonated ester (II). Structure II in Fig. 5 can
rapidly transfer the proton to the carboxylate group that had been the other half of the anhydride linkage.

The mono-addition anhydride (III) can undergo the reaction sequence again to yield either meta or para PMDM. Alternatively, the addition of water can proceed slowly without amine catalysis, and very rapidly with amine catalysis, to yield the mono-addition product (Fig. 6). If the amine catalyst provided sluggish support for the reaction, the aqueous work-up of the reaction mixture yielded quantities of the mono-addition product, in addition to the para and meta isomers. The desired outcome was to have no mono-addition product present.

The rating of the amines was based on the final yield of the para PMDM isomer and the ratio between the para and meta PMDM after three re-crystallizations, as determined by 1H NMR integration (Fig. 3; Table).

Yields of para PMDM depended on: (1) the para/meta ratio in the crude reaction mixture (Table), (2) the addition of HEMA to both of the anhydride linkages, and (3) the separation of all components during washing and crystallization. When all of these factors were favorable, the product melting-point range was 161-162°C and the reaction yield was high.

All of the aliphatic amines were effective in promoting the esterification, but tripropyl- and tributylamines provided mixtures from which it was difficult to extract the para PMDM isomer (Table). This difficulty resulted in less pure products, measured by 1H NMR and melting-point ranges.

The N,N-dimethylbenzylamine was almost as effective as the top three aliphatic amines. Tribenzylamine gave difficulties during crystallization and separation of the para isomer, and NMR spectra of the crude mixture indicated that a significant quantity of the mono-addition product was formed; also, the efficient removal of the catalyst by means of the acid washes did not always occur.

Among the aromatic amines, N,N,N',N'-tetramethyl-1,4-phenylene diamine was judged best, with pyridine in second place due to difficulty in purification. With pyridine, the yield ranked highest of all the amines assayed, but the melting-point range did not.

The amine pKa measures the ability of the nitrogen to donate electrons and stabilize the zwitterionic structure (I, Fig. 5). The catalytically effective pKa range seemed to be between 5.4 (pyridine) and 11.06 (N,N-di-isopropylethylamine; Huenig and Kiessel, 1958). When the pKa was lower, a high percentage of mono-addition product was formed.

With hexamethylenetetramine, DABCO, and pyridine, the carbon atoms neighboring the nitrogen atoms are “tied back”, allowing the lone pair of electrons on each of the nitrogen atoms to be directed outward, promoting rapid reaction with the anhydride. The first two of these amines might most readily partition into the aqueous HCl solutions, facilitating purification.

Why tribenzylamine, N,N-dimethylamine, and triphenylamine formed the large amounts of the mono-addition product (Fig. 6) observed in the crude 1H NMR is not presently understood. A salt of the amine and the acidic intermediate III of Fig. 5 could effectively quench the further reaction. The aqueous work-up of the reaction mixture would then hydrolyze the remaining anhydride linkages to yield the mono-addition product predominantly. A study of the effects of amine and PMDA stoichiometry might elucidate this and other relevant questions.
Fig. 5—The proposed mechanism of the reaction for synthesis of PMDM. The "HOR" can represent most alcohols, but, in this case, it refers only to HEMA. Structure III must undergo the reaction sequence one more time to produce the isomers of PMDM.

Acknowledgment.

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