

Kinetic evaluation of reactivity of bisphenol A derivatives as radical scavengers for methacrylate polymerization

Y. kadoma, S. Fujisawa

Division of Biofunctional Molecules, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University 2-3-10, Kandasurugadai, Chiyoda-ku, Tokyo 101-0062, Japan
 Department of Oral Diagnosis, School of Dentistry, Meikai University, 1-1 Keyakidai, Sakado-shi, Saitama-Ken 350-0283, Japan
 Received 27 October 1999; accepted 22 March 2000

Abstract

The reactivity of bisphenol A (BPA), diethylstilbestrol (DEST), 2,2'-biphenol (22'BP), 4,4'-biphenol (44'BP) and hydroquinone (HQ) as radical scavengers was examined in 2,2'-azobisisobutyronitrile (AIBN)- and benzoyl peroxide (BPO)-induced methyl methacrylate (MMA) polymerization with respect to kinetic considerations. The initial rate of polymerization (IRP) was found to decrease in the order: 44'BP > BPA, DEST > 22'BP > HQ, while the stoichiometric factor (n) of free radicals trapped by phenolic moiety decreased in the order: 44'BP (2.3) > HQ (2.0) > BPA, DEST (1.8) > 22'BP (0.8). It was found that BPA was a more highly efficient inhibitor than HQ and that HQ acts as a retarder at higher concentrations in the BPO system. The high activity of BPA indicated that BPA is probably oxidized by a radical interaction in the dental resin system. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The release of the chemical BPA from light-activated fissure sealants was recently reported [1,2]. BPA is known to be estrogenic at moderate concentration levels [1,2]. Some studies have shown using HPLC analysis that dental sealants and composite resins may be contaminated with BPA [1-3]. BPA from uncured commercial Bis-GMA dental resins is probably found at very low concentration levels using HPLC and/or GC/GM analysis. However, after light-curing sealants, all BPAs have been reported to be undetected as an elute from the tested sealants [4-7].

BPA, a diphenyl compound containing 2 hydroxy groups in para positions [2,2-bis(4-hydroxyphenyl)propane] probably acts as an inhibitor in the polymerization of mono- or dimethacrylates, since compounds such as hydroquinone, which has 2 hydroxy groups in para position, are well-known inhibitors in the polymerization system.

Our studies are based on the hypothesis that the estrogenic BPA in Bis-GMA monomers may be greatly reduced if this compound scavenges radicals derived from the decomposition of the initiator in the resin system. The compound itself is possibly converted into other BPA derivatives due to its radical scavenging reaction in air. The interaction between phenols and peroxy radicals in the presence of oxygen generally yields phenol derivatives due to oxidation [8]. We have previously investigated the kinetics of the polymerization of methyl methacrylate (MMA) by 2,2'-azobisisobutyronitrile (AIBN) or benzoyl peroxide (BPO) in the presence of eugenol using differential scanning calorimetry (DSC), demonstrating

that this method was highly successful and reliable to elucidate the mechanism of a reaction between phenols as antioxidants and radicals derived from the decomposition of the initiators [9].

The present investigation was undertaken to elucidate the reactivity of BPA and its related compounds such as hydroquinone (HQ), 2,2'-biphenol, 4,4'-biphenol and diethylstilbestrol (DEST) in the polymerization of MMA by AIBN or BPO in the presence of air using DSC. Activities of BPA are compared with those of its related compounds.

2. Materials and methods

2.1. Materials

Bisphenol A (BPA), hydroquinone (HQ), 2,2'-bisphenol and 4,4'-biphenol, diethylstilbestrol (DEST), 2,6-di-*t*-butyl-4-methoxyphenol (DTBM), 2,6-di-*t*-butyl-4-methylphenol (butylhydroxytoluene, BHT) were obtained from Tokyo Kasei Chemical Co., Tokyo, Japan. MMA was purchased from Tokyo Kasei Chemical Co. and was purified by distillation. AIBN and BPO were obtained from Wako Pure Chemical Industries Ltd. and recrystallized from methanol and chloroform/methanol, respectively. The chemical structure of BPA-related compounds is shown in Fig. 1.

2.2. Methods

The experiments were performed using a DSC in a similar manner as previously reported [9]. About 10 μ l

[MMA: 9.12-9.96mg] of the experimental resin with indicated initiators and/or inhibitors was loaded into an aluminium sample container and sealed by applying pressure. The container was placed in a differential scanning calorimeter (model DSC 3100 MAC Science Co., Tokyo, Japan).

2.3. Measurement of initiation rate, Ri

The induction period method was used to determine Ri due to the thermal decomposition of AIBN, by using $R_i = n[IH] / IP$, (1) where [IH] is the concentration of the inhibitor at time zero and IP is the induction period (IP). DTBM was used to determine Ri, since its stoichiometric factor n, is known to be 2.00 [10]. The value of induction period, IP, was determined graphically from the plot of the conversion versus time, as the point of intersection of the first linear line of the conversion rate of polymerization of MMA with time axis after the inhibitor was consumed. In the case of [MMA] = 9.4 mol/l and [AIBN] = 0.1 mol/l, the inhibitor method using DTMP (five different concentrations between 10^{-4} and 10^{-2} mol/l) gave the rate initiation Ri (5.66 ± 0.48) $\times 10^{-6}$ mol/l s at 70 °C.

2.4. Measurement of stoichiometric factor (n)

Relative n values in Eq. (2) can be calculated from the induction periods in the presence of phenol additives as an inhibitor [8,10].

$$n = n[IH]/R_i \quad (2)$$

where IP is the induction period (IP), Ri is the rate of initiation and [IH] represents an inhibitor. The number of moles of peroxy radicals trapped by moles of the relevant phenol inhibitor, n values were calculated with respect to one unit of phenolic moiety.

2.5. Measurement of initial rate of polymerization (IRP)

The initial rate of polymerization inhibited by BPA and related compounds was calculated from the slope of the plots of first linear line of the conversion rate of polymerization of MMA shown in Figs. 2 and 3. The conversion of control and BPA-related compounds in the both AIBN and BPO system was 94.3-96.9%. The conversion of 100% corresponds to 9.4 mol/l MMA polymerizing. The heat of polymerization of MMA was $13.0 \text{ Kcal mol}^{-1}$ in this experiment.

3. Results

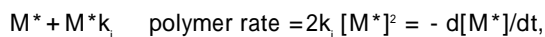
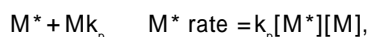
3.1. polymerization of MMA by AIBN

Some typical conversion-time curves of BPA, DEST and HQ initiated with AIBN and BPO in air are shown in Figs. 2 and 3, respectively. The polymerization curves show a break when the inhibitor was completely consumed.

These breaks are very sharp and provide a very reliable measure of IP and IRP. The IP and IRP values as a function of the concentration of BPA and related compounds, initiated with AIBN and BPO are shown in Figs. 4-7.

polymerization in the control was inhibited, even though the reaction was carried in the sealed DSC pan, which contained a small amount of oxygen because it was sealed in air. The presence of oxygen inhibits polymerization because oxygen as a diradical reacts with free radicals generated by AIBN or BPO. During the initial period, the polymerization becomes almost completely suppressed by oxygen or BPA and related compounds and following this period the polymerization is much more rapid. BPO is known to show an induced decomposition in the initiation of polymerization and, therefore, the kinetics of the inhibitory effects were studied in the AIBN system. Table 1 shows the initial rate of polymerization (IRP) with varying the concentrations of AIBN. The findings in Table 1 indicate that the polymerization reaction proceeds according to the rate expression (3), which is the most common formula for polymerization reactions [10].

The rate constants for propagation, k_p , and for termination, k_t , are defined by the reactions



where M is the monomer, and M^* the growing polymer radical.

$$IRP = k_p/(2k_t)^{1/2}[MMA]R_i^{1/2} \quad (3)$$

Eq. (3) is known to be derived from the chain reaction, in which R_i represents the rate of initiation (2). The $IRP/[MMA]R_i^{1/2}$, $k_p/(2k_t)^{1/2}$ values were constant, 9.86 ± 0.97 (Table 1) within the limit of experimental error despite changes in the concentration of AIBN. Therefore, we next investigated the inhibitive activity of BPA-related compounds based on kinetic studies, namely to measure the inhibition rate (initial rate of polymerization) and inhibiting period (induction period) of polymerization.

3.2. Induction period (IP) and initial rate of polymerization (IRP) of BPA and related compounds in the AIBN-induced polymerization

Plots of the induction period [IP of test compound (IP_t)-IP of control (IP_c)] versus concentrations of bisphenol A and related compounds of AIBN polymerization are shown in Fig. 4. The linear curves of the values of the IP_t-IP_c were obtained in DTBM and HQ. The curves of 22'BP, BPA, DEST and 44'BP were parabolic and were not proportional to their higher concentration of 0.10 mol%.

Fig. 5 shows a plot of the IRP versus the concentration of BPA and related compounds. The IRP of BPA, DEST, DTBM and 44'BP was slightly decreased as their concentration increased, however, the line appeared to be parallel to the abscissa above a concentration of 0.02 mol%

, indicating that they did not affect the initiation of AIBN. This was consistent with the generally known kinetic findings of AIBN polymerization. Whereas, IRP of HQ and 22'BP were decreased dose-dependently, and in particular HQ was strongly reduced. This indicated that HQ acted as a retarder in MMA polymerization.

3.3. Stoichiometric factor (n) for BPA and related compounds

The relative n value (stoichiometric factor) for BPA and its related compounds at 0.05 mol% was calculated from the findings for IP shown in Fig. 3 using Eq. (2). The n value for 22'BP, 0.82, was found to be considerably lower than that for 44'BP, 2.33, indicating an activity difference between the 0-0' and p-p' phenol dimer. The n values of BPA, DEST and HQ were 1.82, 1.77 and 1.95, respectively (Table 2). Their n values were very close to 2.0.

3.4. BPO-induced polymerization reactions in the presence of BPA and related compounds

Plots of $IP_i - IP_c$ versus concentrations of bisphenol A and related compounds of BPO polymerization are shown in Fig.6. Compared with the linear curve of DTBM, the curves of BPA, DEST, BHT and HQ were parabolic. It was clear that IP of DEST and BPA was higher than that of BHT and HQ, IP of HQ was markedly smaller than that of other compounds at concentrations >0.05 mol%.

The plots of IRP versus concentrations of BPA, DEST, BHT, DTBM and HQ are shown in Fig.7. The IRP of HQ was more strongly reduced than that of other compounds. Comparing IRP of BPA, DEST and HQ in the AIBN system, their IRP became markedly reduced as their concentration increased.

4. Discussion

From the findings mentioned above, BPA clearly acted as an inhibitor in both AIBN and BPO-induced MMA polymerization. In particular, BPA was an efficient inhibitor in BPO-induced MMA polymerization. This activity was significantly higher than that of HQ. Also, the IP of BPA was larger than that of butylhydroxytoluene (BHT), a widely known inhibitor. The relative n value of BPA in the AIBN system was close to 2.0 and was almost a similar value to that of HQ. This suggests that BPA suppressed the polymerization and scavenged radicals derived from the decomposition of initiators in the polymerization system.

Numerous factors and conditions influence the BPA elution process from sealant and composite materials. In a clinical dental setting, the depth of cure, intensity of light and curing time would all affect the BPA elution [11]. Our findings suggested a particular inhibitory effect of the oxygen in air on the polymerization of methacrylates. However, the present findings indicated that even though

BPA is contaminated in Bis-GMA monomer during the synthesis of Bis-GMA, it would be strongly reduced after its curing due to radical scavenging. Also, after the setting of Bis-GMA resins, BPA would not exist as BPA itself, but as its derivatives due to the reaction between BPA and radicals derived from the decomposition of the polymerization initiators. This suggests that human infertility, genital tract malformation might not be linked with BPA eluted from Bis-GMA sealants and composite resins [1].

As shown in the HQ' conversion-time curve in both AIBN and BPO-induced MMA polymerization (Figs. 1 and 2), the break in the HQ' curve was less sharp than that of BPA and DEST, resulting in a decrease in IRP. It is unknown whether the HQ radical is able to initiate as well as stop chains in the presence of the very reactive MMA molecule. There are two cases, one where the inhibitor radical stops one growing chain and other where the inhibitor radical may start a chain by a reaction between the inhibitor radical and MMA. One can calculate the degree of the initiation by the inhibitor from the measurements shown in Fig. 4. If the HQ does not initiate a chain, the relation between the ratio of concentrations of HQ and the corresponding IP ratio should be identical. As indicated in Fig. 4, in the AIBN system, a straight line for HQ is shown, similar to that of DTBM. Despite an identical reaction of HQ between the IP and concentrations, the IRP of HQ was strongly reduced dose-dependently, suggesting that semiquinone (SQ) radicals derived from HQ affect chain propagation of the activated MMA molecule. In the BPO system, HQ showed the smallest IP and the largest decrease in IRP among test compounds. This implies that one or more HQ oxidation products (i.e. SQ) can also react with peroxy radicals and/or MMA peroxide from an oxygen effect in MMA polymerization [12].

It has previously been shown that BQ (benzoquinone) radicals from HQ or eugenol radicals are easily detected in alkaline conditions, whereas BPA radicals are not found in strong alkaline conditions using ESR spectroscopy [13,14]. Also, it was previously demonstrated that eugenol in BPO-induced MMA polymerization showed a decrease in IRP. Therefore, a decrease in IRP appears to be linked to a reaction between inhibitor radicals and growing radicals. In conclusion, BPA acted not as a retarder but as an inhibitor, and its activity was higher than that of HQ or BHT in the BPO system. BPA may be changed into its quinone derivatives due to oxidation by radicals in methacrylate polymerization. This investigation has been performed as a model system. However, the predictions are considered to be quite accurate in a higher viscosity monomer of Bis-GMA than that of MMA.