CODEN IEJMAT *Internet Electronic Journal of Molecular Design* **2005**, *4*, 711–720 ISSN 1538–6414
BioChem Press http://www.biochempress.com

Inter*net* Electronic Journal of
Molecular Design

October 2005, Volume 4, Number 10, Pages 711–720

Editor: Ovidiu Ivanciuc

Special issue dedicated to Professor Danail Bonchev on the occasion of the 65th birthday

Antioxidant Activity of Diphenylamine–Related Compounds as Scavengers of Carbon Radicals

Seiichiro Fujisawa,[1] Mariko Ishihara,[1] and Yoshinori Kadoma [2]

[1] Meikai University School of Dentistry, 1–1 Keyakidai, Sakado, Saitama 350–0283, Japan
[2] Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2–3–10 Kanda–Surugadai, Chiyoda–Ku, Tokyo 101–0062, Japan

Received: October 6, 2004; Revised: January 27, 2005; Accepted: April 4, 2005; Published: October 31, 2005

Citation of the article:
S. Fujisawa, M. Ishihara, and Y. Kadoma, Antioxidant Activity of Diphenylamine–Related Compounds as Scavengers of Carbon Radicals, *Internet Electron. J. Mol. Des.* **2005**, *4*, 711–720, http://www.biochempress.com.

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Antioxidant Activity of Diphenylamine–Related Compounds as Scavengers of Carbon Radicals

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[2] Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2–3–10 Kanda–Surugadai, Chiyoda–Ku, Tokyo 101–0062, Japan

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Abstract

Motivation. Diphenylamine–related compounds, which are singlet oxygen scavengers, have been utilized as antioxidants. Quantitative *in vitro* studies of these amine antioxidants and their inhibition of autooxidation have been performed under aerobic conditions, but the relevance of these studies to biological systems is unclear. Since biological systems have low oxygen tensions, the effectiveness of amine antioxidants may differ markedly between nonbiological and biological conditions. Kinetic studies of radical scavenging by phenylamines are needed to clarify this point. Also, the ability of these antioxidants to scavenge carbon–centered radicals remains unknown. In the present study, we evaluated the efficiency of radical scavenging by the diphenylamine–related compounds.

Method. Polymerization of methyl methacrylate initiated by AIBN in the presence or absence of amine antioxidants was studied by DSC at 70°C. Time–exotherm curves were used to determine time–conversion curves, and IP, Rp_{con} and Rp_{inh} were determined.

Results. A linear relationship between the length of the IP and the concentration of antioxidants was obtained. Also, values of Rp_{inh}/Rp_{con} decreased linearly as the concentration increased. The *n* values for DPPD, HDPA and MEAN were approximately 2, 2 and 1, respectively. Rp_{inh}/Rp_{con} values declined in the order MEAN > DPPD > HDPA. In particular, HDPA markedly decreased the Rp_{inh}/Rp_{con} value, *i.e*. the KCL. k_{inh}/k_p was calculated from IP and Rp_{inh}/Rp_{con}, and the value declined in the order MEAN (11.6) > HDPA (6.8) > DPPD (4.2).

Conclusions. HDPA, DPPD and MEAN are efficient scavengers of carbon–centered radicals derived from AIBN. In particular, HDPA strongly suppresses growing MMA radicals, probably because of formation of semiquinone radicals and, consequently, phenyl–1,4–benzoquinonemonoimine. The k_{inh} for MEAN was about twice that for DPPD or HDPA. Previously reported k_{inh} values for DPPD in reactions with linoleic acid peroxy radicals and poly (styryloperoxy) radicals are much higher than that determined in the present study. Although the methodologies of these studies were rather different, the discrepancy is probably due to differences in oxygen tension. Biomimetic evaluation of antioxidants should be performed under low oxygen tension.

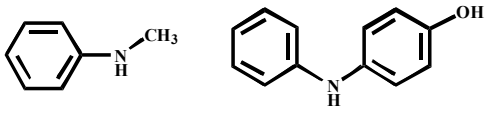
Keywords. Phenylamines; antioxidants; stoichiometric factors (*n*); inhibition rate constants.

Dedicated on the occasion of the 65th birthday to Danail Bonchev.

* Correspondence author; E–mail: fujisawa@dent.meikai.ac.jp.

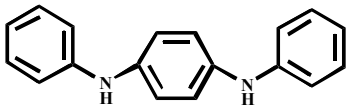
1 INTRODUCTION

Amine antioxidants, especially oil–soluble secondary diphenylamines such as DPPD and HDPA, have been widely used as stabilizers in nitrocellulose–containing explosives and propellants and in the rubber and elastomer industry. Diphenylamines are also widely used to prevent post–harvest deterioration of apple and pear crops. Thus, these compounds present a potential environmental hazard [1]. However, studies on their kinetic radical–scavenging activity are very sparse [2–4]. We have previously reported use of induction period methods to evaluate the radical–scavenging ability of polyphenols [5], beta–carotene [6], butylated hydroxytoluenes [8] and miscellaneous natural and synthetic antioxidants [8]. In the present study, we used these methods to investigate the radical MMA initiated by thermal decomposition of AIBN. For DPPD, HDPA and MEAN, n and R_{inh} were determined. The kinetic effects of amine antioxidants are discussed from the perspective of the N–H and/or O–H bond dissociation energies of phenoxyl and aminyl radicals from phenylamines.



MEAN

HDPA



DPPD

2 MATERIALS AND METHODS

Antioxidants were purchased from Tokyo Kasei Co, Tokyo, Japan. MMA was purified by distillation. AIBN was recrystallized from methanol.

2.1 Chemical Data

2.1.1 Stoichiometric factor (*n*)

The *n* values were determined by the induction period method previously reported [7,8]. Figure 1 shows exothermic and time–conversion curves. In brief, the experimental resin consisted of MMA and AIBN with or without antioxidants or radical scavengers, *i.e.* inhibitors. The concentration of AIBN was 1 mole% and that of the inhibitors was 0–0.5 mole%. About 10 microL of the experimental resin (MMA) was loaded into an aluminum sample container, which was sealed by applying pressure. The container was placed in a differential scanning calorimeter (model DSC 3100; MAC Science Co., Tokyo, Japan) maintained at 70°C. Time–exotherm curves for each compound are shown in Figure 1 (top).

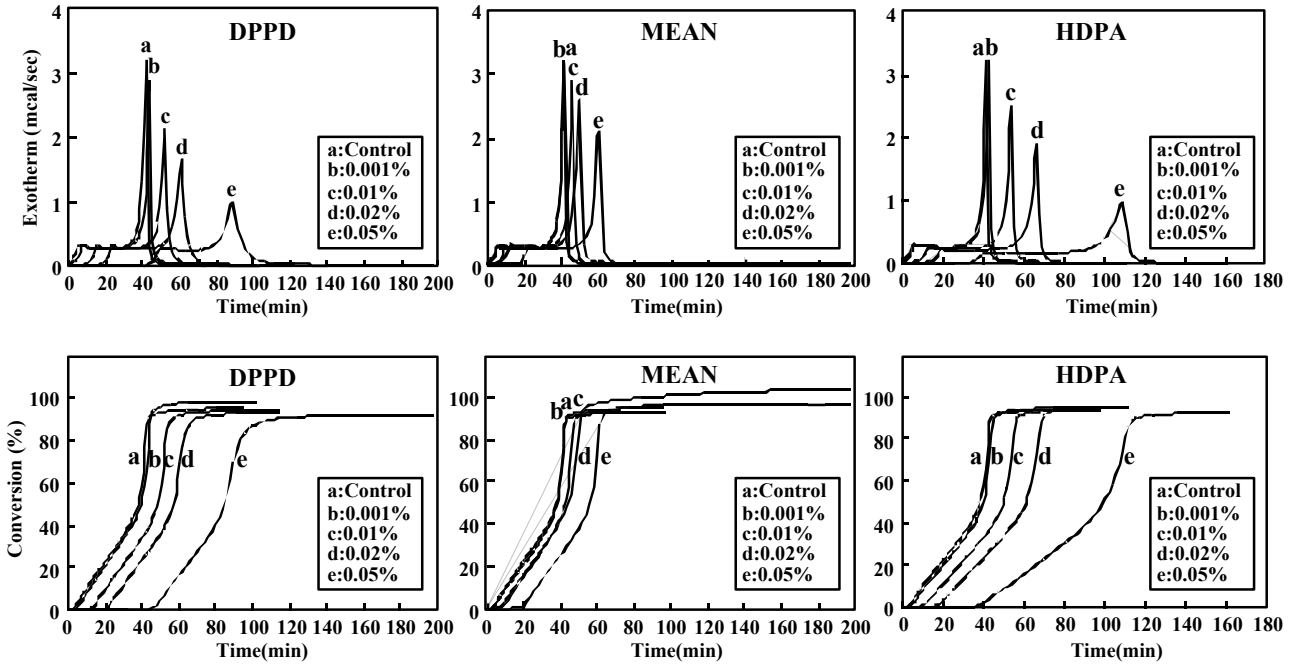


Figure 1. Exothermic (top) and time–conversion curves (bottom) for the polymerization of MMA–AIBN in the presence of phenylamine compounds.

Thermal changes induced by polymerization of MMA were 13.0 kcal/mole in this experiment. Polymerization curves were derived from DSC thermograms of the integrated heat evoked by polymerization of MMA. Curves for inhibitors in the AIBN system are shown in Figure 1 (bottom). The time–conversion curves in the absence (control) and the presence of inhibitors showed a break when the additives had been completely consumed. These breaks were sharp and provided a reliable measure of the induction (inhibition) period and initial rate of polymerization. Such a break was detected in the absence of inhibitor (control) because oxygen acts as an inhibitor. In the present study, the IP for test compounds is presented as the difference from controls. Tangents were drawn to polymerization curves at an early stage in the run, and the IP was determined from the length of time between the zero point on the abscissa and the point of the intersection of tangents drawn to the early stage of polymerization. IP values for test compounds were calculated as differences in IP between the test compounds and the controls. *n* values were calculated per one unit of phenolic moiety by using Eq. (1):

$$n = [\mathrm{IP}]R_i/[\mathrm{IH}] \quad (1)$$

in which R_i (the rate of initiation) for AIBN was 5.66×10^{-6} $\mathrm{Ml^{-1}s^{-1}}$ at 70°C. These R_i values were determined by the induction period method using 2,6–di–*tert*–butyl–4–methoxyphenol (DTBMP) with a stoichiometric factor of 2.00 [2]. IH represents inhibitor.

2.1.2 Inibition rate constant (k_{inh})

The k_{inh} values were calculated from the equations described below. The initial rate of polymerization (Rp_{con}) and the inhibited rate of polymerization (Rp_{inh}) were calculated from the

slope of the first linear portion of the conversion rate of polymerization of MMA (Figure 1). Rp_{con} and Rp_{inh} were calculated from Eq. (2) and Eq. (3), respectively [2,3,7–9]:

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

$$Rp_{inh} = \{k_p\ [MMA]\ R_i \}/\{n\ k_{inh}\ [IH]\} \quad (3)$$

where k_p and k_t represent the rate constants of propagation and of termination, respectively, and MMA is methyl methacrylate.

The rate of decrease in polymerization curves can be expressed by Eq. (4):

$$Rp_{inh}/Rp_{con} = \{(2\ k_t\ R_i)^{1/2}\}/\{n\ k_{inh}\ [IH]\} \quad (4)$$

Eq. (2) and Eq. (4) can be rearranged to calculate k_{inh}/k_p.

$$k_{inh}/k_p = [MMA]/\{[IP] \times [Rp_{inh}]\} \quad (5)$$

2.1.3 PM3 calculation

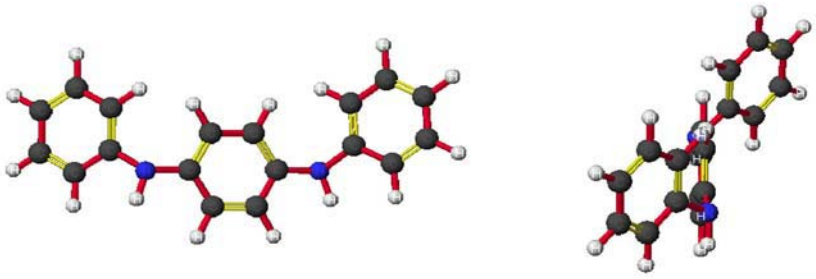
The polarity of the medium plays an important role in determining the solvent effect on the conformational equilibrium [9]. Aromatic secondary amines might have both the sub–optimum conformation in polar mediums (high dielectric constant solvents such as water) and the optimum conformation *in vacuum* (or low dielectric constant medium such as chloroform).

Theoretical calculation were carried out at the restricted Hartree–Fock level (RHF) PM3 semiempirical method, as implemented in the MOPAC 2000 program on a Tektronix CAChe Work station. Solvent effects for secondary amines were calculated using the COSMO methodology. We used the medium's dielectric constant, $\varepsilon = 78.4$ for water as solvent and $\varepsilon = 1.0$ for gas phase (vacuum). The BDE for secondary amine compounds was calculated using COSMO (water) and non–COSMO (vacuum). Geometry optimization was performed using CONFLEX and based on the approach, the heats of formation for each compound for COSMO and non–COSMO were calculated using CAChe Work System. In order to simplify calculation, the BDE for DPPD, HDPA, and MEAN when the H atom is tentatively abstracted by 5 Å from the –H and/or O–H bond was determined. The geometry for MEAN, HDPD and DPPD is illustrated in Figure 2.

3 RESULTS AND DISCUSSION

Figure 3 shows the relationship between induction period and concentration for amine antioxidants. Linear relationships were found for each compound (Figure 3A). The *n* values for DPPD and HDPA were about 2, whereas that for MEAN was approximately 1. Next, the relationship between Rp_{inh}/Rp_{con} and concentration was investigated (Figure 3B). For all

compounds, Rp_{inh}/Rp_{con} decreased linearly as the concentration increased, but the slope for HDPA was much steeper than that for DPPD or MEAN. An *n* value for DPPD of about 2 has been reported from a study using an induction period method in the styrene–chlorobenzene system with thermal decomposition of AIBN at 30°C under 760 torr of O_2 [3]. Also, although the data are fairly old, the *n* values for MEAN, DPPD and HDPA have been reported to be 2.0, 2.2 and 2.1, respectively, by an induction period method involving the oxidation of cumene in chlorobenzene initiated by thermal decomposition of AIBN at 62.5°C under aerobic conditions [4]. Furthermore, *n* values for DPPD have been determined in SDS micelle solution by decomposition of 2,2'–azobis (2–amidinopropane) dihydrochloride at 37°C, yielding an *n* of 1.84 [2].



DPPD

HDPA

MEAN

Figure 2. Geometry of DPPD, HDPA and MEAN in water (e=78.4) calculated by the PM3/COSMO method. The structure of MEAN was planar, whereas that for DPPD and HDPA was a twisted form.

The stoichiometric factor of HDPA for reaction with R• (cyanoisopropyl) radicals from AIBN in the present study coincided with that previously reported for the reaction with ROO• radicals under aerobic conditions, whereas the stoichiometric factors for DPPD and MEAN were different from

those previously reported. In general, DPPD should show a clean stoichiometry of 2 [4]; however, in the present study DPPD gave non–integral stoichiometry (*n* ~2.5), possibly because of further oxidation of quinoimines produced by radical oxidation of DPPD.

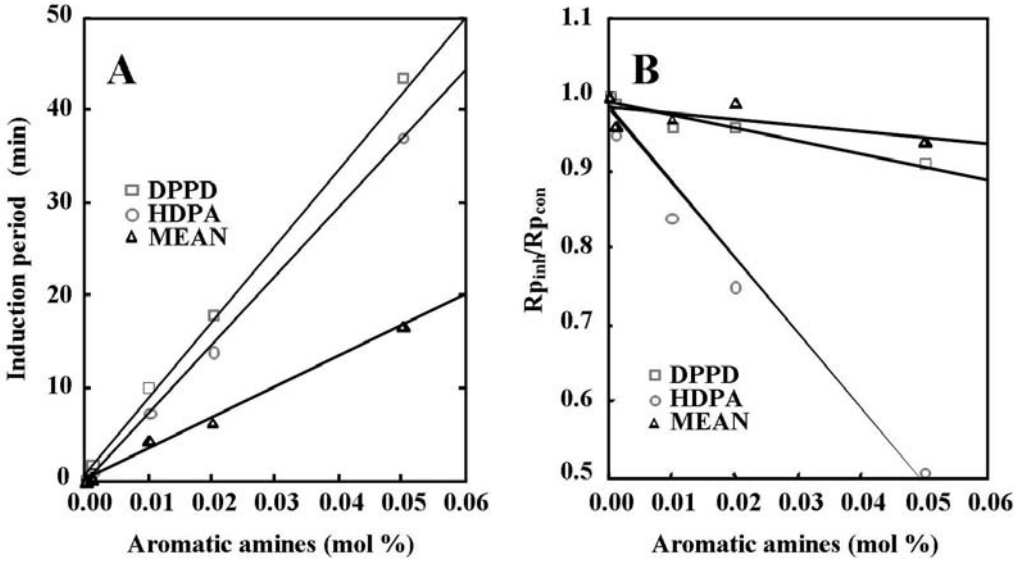


Figure 2. Plots of the induction period (A) and Rp_{inh}/Rp_{con}(B) *vs*. concentrations of phenylamines.

A reaction giving products that are themselves inhibitors would lead to higher *n* values [9]. The *n* value of 1 for MEAN was not in agreement with that of a previous report [4]. Recently, we demonstrated that DPPD is considerably less likely to react with PhCOO• radicals derived from benzoyl peroxide (BPO), which is assumed to arise from the lower potency of hydrogen abstraction by BPO from these secondary amines [8].

The radical–scavenging activity of phenylamine secondary amines in the BPO system presents special and complicated problems that are not resolved on the basis of stoichiometry alone, since hydrogen abstraction is not the first step in reaction with most inhibitors. This may be due to the lower R_i value of BPO (2.28×10^{-6} Ms^{-1}) compared with that for AIBN, the R_i for BPO may have an effect on the stoichiometry. We estimated the quantity of oxygen in the DSC container in the present study to be about 8.12×10^{-8} mol.

The k_{inh}/k_p values for the aromatic amines were calculated from Eq. (5). The k_{inh}/k_p values for DPPD, HDPA and MEAN were 4.2, 6.8 and 11.6, respectively. The k_{inh} for DPPD was compared with values previously reported [2,3]. (Note that the k_p value for MMA of 575 $M^{-1}s^{-1}$ at 60°C was used for that at 70°C, because the k_p of MMA at 70°C is unknown but was assumed to be close to the value at 60°C [5].) The k_{inh} value of DPPD for the reaction with poly–MMA radicals in the

present study was about 2.4×10^4 $M^{-1}s^{-1}$. In contrast, the previously reported k_{inh} value of DPPD for the reaction with linoleic acid peroxy radicals was 15×10^4 $M^{-1}s^{-1}$ [2] and that for the reaction with poly(styryloperoxy) radicals was approximately 117×10^4 $M^{-1}s^{-1}$ [4].

Comparing the findings for polymer radicals, the k_{inh} value of DPPD for the reaction with poly (styryloperoxy) radicals was about 460–fold greater than that for the reaction with poly–MMA radicals in the present study. The formation of DPPD radicals under aerobic conditions is in accordance with the belief that DPPD has close to optimal properties for trapping peroxy radicals. Thus, since the *n* value for DPPD would be rather low, the k_{inh} value for DPPD would be enhanced, as indicated by Eq (4). Similarly, the finding of the relatively lower k_{inh} value for DPPD in the present study may be attributed to the observed *n* value, > 2. The k_{inh} values for HDPA and MEAN were 3.96×10^4 $M^{-1}s^{-1}$ and 6.6×10^4 $M^{-1}s^{-1}$, respectively. The k_{inh} for MEAN was double that for DPPD or HDPA. The k_{inh} of diphenylamine for the reaction with poly (styryloperoxy) radicals at 65°C has previously been reported to be 2×10^4 $M^{-1}s^{-1}$ [10,11]. This value for diphenylamine appears to be similar to that for HDPA.

Absolute inhibition rate constants for the secondary amine DPPD in the present study were markedly lower than those previously reported. Although the methodologies of these studies were rather different, this large discrepancy in the k_{inh} for DPPD may be due to the presence of oxygen, because DPPD has a high affinity for oxygen [12]. The effects of oxygen on the radical–scavenging activity of antioxidants have previously been reported, demonstrating that at low oxygen tensions the well–known antioxidants ascorbate and vitamin E are very poor radical scavengers of carbon–centered radicals derived from azo–initiators [13] and focusing attention on the activity of molecular oxygen as a biradical.

HDPA strongly decreased the Rp_{inh}/Rp_{con} value, *i.e*. the KCL, as its concentration increased, suggesting an inhibitory effect of HDPA on growing MMA radicals. This is probably due to the production of semiquinone radicals and, consequently, formation of phenyl–1,4–benzoquinonemonoamines [14]. We have previously shown that the formation of quinones can suppress growing MMA radicals [7], and inhibitory effects of quinones on lipid peroxidation have been demonstrated [15]. Similarly, the formation of iminoquinones derived from oxidation of DPPD suppresses growing MMA radicals, but to a lesser extent (Figure 3B).

The dissociation of chemical bonds constitutes a crucial concept in our understanding of chemical transformations. The N–H bond dissociation energy (BDE_{NH}) for HDPA, DPPD and MEAN was calculated by the PM3 semiempirical method (non–COSMO). The BDE_{NH} (kcal mol^{-1})

for HDPA, DPPD and MEAN is 94.89, 169.99, and 105.51, respectively, whereas the heat of formation (kcal mol^{-1}) of the corresponding compounds is 9.25, 79.35, and 20.68, respectively. In contrast, the BDE_{OH} (kcal mol^{-1}) of HDPA when the H atom is tentatively abstracted by 5 Å from the O–H bond is 89.35.

Thus, abstraction of the H atom from the O–H group of HDPA occurs preferentially. Experimentally determined values of the BDE for the N–H and O–H bonds in HDPA have been reported recently [14]: for HDPA, BDE_{NH} = 84.68 kcal mol^{-1} and BDE_{OH} = 81.69 kcal mol^{-1}, and for its semiquinone radical BDE_{NH} = 65.39 kcal mol^{-1} and BDE_{OH} = 62.02 kcal mol^{-1}. Although the found and calculated BDE values for HDPA are different, the experimental values still support preferential abstraction of H atoms from O–H groups, which would subsequently lead to formation of semiquinone radicals. Similarly, experimentally determined BDE values for the N–H bonds have been reported previously: for MEAN, BDE_{NH} = 67.7 kcal mol^{-1} (73.3 kcal mol^{-1} by DFT–AM1)[16] and diphenylamine, BDE_{NH} = 87 kcal mol^{-1} in benzene [17], respectively. From the Ref. [17], the BDE_{NH} for DPPD with two N–H bonds in its molecule is assumed to be about 174 kcal mol^{-1}.

DPPD is a more effective antioxidant in aqueous micellar solutions, whereas this is not true in organic solutions, possibly because DPPD, a secondary amine, is partially protonated [2]. Thus, the BDE for HDPA, DPPD and MEAN in COSMO was calculated by the PM3 method. The BDE_{NH} (kcal mol^{-1}) for HDPA, DPPD and MEAN is 83.91 (BDE_{OH} = 74.18 kcal mol^{-1}), 159.79 and 99.05, respectively. The heat of formation (kcal mol^{-1}) of the corresponding compounds is –4.15, 70.12, and 15.50. The BDE and heat of formation values for COSMO are considerably smaller, by about 10%, than those for non–COSMO. The reactivity of amines may be more pronounced in more polar environments [2]. To say more precisely, the calculated BDE of HDPA and MEAN for COSMO have been close to their experimentally determined one.

Conversely, the calculated BDE of DPPD for non–COSMO has been close to the BDE that is estimated from the cited value of diphenylamine [17]. This may be attributable to the hydrophobicity (log P, Hansch π [18]) of these compounds. The hydrophobicity (log P) declines in the order of DPPD (4.70) > HDPA (2.66) > MEAN (1.46). Although a relatively great variation of the BDE between the experimental and the PM3–calculated values has been found, a qualitative comparison has been acceptable in the present study. The BDE_{NH} for DPPD was about two times greater than that for MEAN, judged by the PM 3 results. In contrast, the *n* value for the former was about 2, whereas that for the latter was 1. The *n* value may be attributable to the BDE. MEAN with *n* = 1 provably undergo dimerization due to the radical coupling reaction.

4 CONCLUSIONS

Diphenylamine–related compounds, which are singlet oxygen scavengers, have been utilized as antioxidants. Quantitative *in vitro* studies of these amine antioxidants and their inhibition of autooxidation have been performed under aerobic conditions, but the relevance of these studies to biological systems is unclear. Since biological systems have low oxygen tensions, the effectiveness of amine antioxidants may differ markedly between nonbiological and biological conditions. Kinetic studies of radical scavenging by phenylamines are needed to clarify this point. Also, the ability of these antioxidants to scavenge carbon–centered radicals remains unknown. In the present study, we evaluated the efficiency of radical scavenging by the diphenylamine–related compounds.

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A linear relationship between the length of the IP and the concentration of antioxidants was obtained. Also, values of Rp_{inh}/Rp_{con} decreased linearly as the concentration increased. The *n* values for DPPD, HDPA and MEAN were approximately 2, 2 and 1, respectively. Rp_{inh}/Rp_{con} values declined in the order MEAN > DPPD > HDPA. In particular, HDPA markedly decreased the Rp_{inh}/Rp_{con} value, *i.e*. the KCL. k_{inh}/k_p was calculated from IP and Rp_{inh}/Rp_{con}, and the value declined in the order MEAN (11.6) > HDPA (6.8) > DPPD (4.2).

HDPA, DPPD and MEAN are efficient scavengers of carbon–centered radicals derived from AIBN. In particular, HDPA strongly suppresses growing MMA radicals, probably because of formation of semiquinone radicals and, consequently, phenyl–1,4–benzoquinonemonoimine. The k_{inh} for MEAN was about twice that for DPPD or HDPA. Previously reported k_{inh} values for DPPD in reactions with linoleic acid peroxy radicals and poly(styryloperoxy) radicals are much higher than that determined in the present study. Although the methodologies of these studies were rather different, the discrepancy is probably due to differences in oxygen tension. Biomimetic evaluation of antioxidants should be performed under low oxygen tension.

Acknowledgment

The authors acknowledge the financial of this research by a Grand–in–Aid from the Minister of Education, Science, Sports, and Culture of Japan.

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Biographies

Seiichiro Fujisawa is Professor of Dentistry and Chairman of the Department of Oral Diagnosis at Meikai University. His major research projects are the free radical mechanisms of toxicity, catalysis and protection.

Mariko Ishihara is a chemist and lecturer at Meikai University School of Dentistry.

Yoshinori Kadoma is a chemist and Associate Professor at Tokyo Medical and Dental University Institute of Biomaterials and Bioengineering. His major research projects are preparation and evaluation of synthetic medical polymers.