Factors Influencing the Antioxidant Activities of Phenols by an Ab Initio Study

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An ab initio molecular orbital theory has been applied to the elucidation of the hydrogen abstraction mechanism of phenolic antioxidants in the chain process of autoxidations. The optimum structures of o-, m-, and p-substituted phenols, of peroxides, and of those compounds in the transition states were obtained with a Hartree-Fock/STO-3G basis set. From the values of the enthalpy (ΔH), activation (E_a), and OH bond dissociation ($D(\text{O–H})$) energies obtained, it was found that these three parameters indicate a good relationship with each other; particularly, the relation between the ΔH and E_a values follows the Evans-Polanyi rule. The electron-releasing substituents in the o- and p-positions in phenols decrease the activation parameters for hydrogen abstraction, while those in the m-position increase. The electron densities on the ipso-carbon, oxygen, and hydrogen of the OH substituent and their bond populations are obtained. Variations of the electron densities from the reactants to the transition states lead to a clarification of the reaction mechanism as an antioxidant. Namely, the gain or loss of electrons in the reaction states may be correlated to the experimental data, ^{13}C chemical shifts of the ipso-carbon of the OH substituent, and the values of the induction period as an antioxidant activity.

Recently, we reported on a study of the hydrogen abstraction of phenolic antioxidants in the chain process of autoxidation, by means of ab initio molecular orbital calculations.[1] Such antioxidants as phenol derivatives react as chain-breaking inhibitors of the peroxyl radical,

$$XOO\cdot + ArOH \longrightarrow XOOH + ArO\cdot,$$
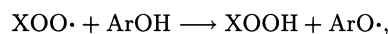
where XOO· denotes the peroxyl radical and ArOH represents antioxidant phenols. Subsequently, para-substituted phenols in hydrogen abstraction by XOO· radicals are investigated in detail. In 1947, Bolland and Ten Have[2] concluded that antioxidants react with peroxyl radicals and not with alkyl radicals. This conclusion agrees with the results of our calculations, which support the idea that the initial channel of the chain-breaking inhibition by antioxidants is a reaction with the XOO· radical.

In this study, first, further examinations of the reaction mechanism with the peroxyl radicals are investigated in detail from the standpoint of the activation parameters, ΔH, E_a, and $D(\text{O–H})$ values. The obtained data are also discussed concerning substituent effects, on the basis of Structure I in the transition state and the various substituents, R and X, as shown in Scheme 1.

In our previous papers it was reported that the antioxidative activities of twenty compounds of four series of benzylphenols[3] and nineteen compounds of seven series of alkylidene- and benzylidenebisphenols[4] were evaluated by means of an oxygen-absorption method at 60°C for tetralin. In particular, the activities exhibited by the induction period (IP) were found to closely correlate with the ^{13}C chemical shifts of the ipso-carbon of the OH substituent, as can be seen in Fig. 1. This fact indicates that the IP values increase with a decrease in the chemical shifts, and that the electron density on the ipso-carbon of the OH substituent does affect the
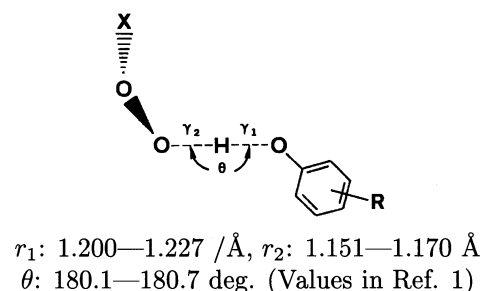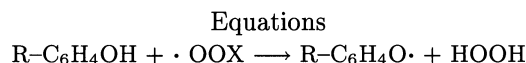

r_1: 1.200—1.227 /Å, r_2: 1.151—1.170 Å

θ: 180.1—180.7 deg. (Values in Ref. 1)

Chart 1. Structure I.

Equations

$$R\text{–}C_6H_4OH + \cdot OOX \longrightarrow R\text{–}C_6H_4O\cdot + HOOH$$

Eq.	R	X	Eq.	R	X
1	H	H	9	p-CH₃	H
1a	H	CH₃	10	p-NH₂	H
2	o-CH₃	H	10a	p-NH₂	CH₃
3	o-NH₂	H	11	p-OH	H
4	o-OH	H	12	p-OCH₃	H
5	m-CH₃	H	12a	p-OCH₃	CH₃
6	m-NH₂	H	13	p-F	H
7	m-OH	H	14	p-Cl	H
8	m-F	H	14a	p-Cl	CH₃

Scheme 1. Structure I and Equations.

antioxidant activity.

Next, the electron densities of the ipso-carbon, oxygen, and hydrogen atoms of the OH substituents in phenols were calculated. These data varied through the reaction states, that is, the reactants, transition, and product states. In order to further elucidate the antioxidant mechanism, we will discuss the relations between the variations of the electron densities and the activities as phenolic antioxidants, based on the substituent effects.
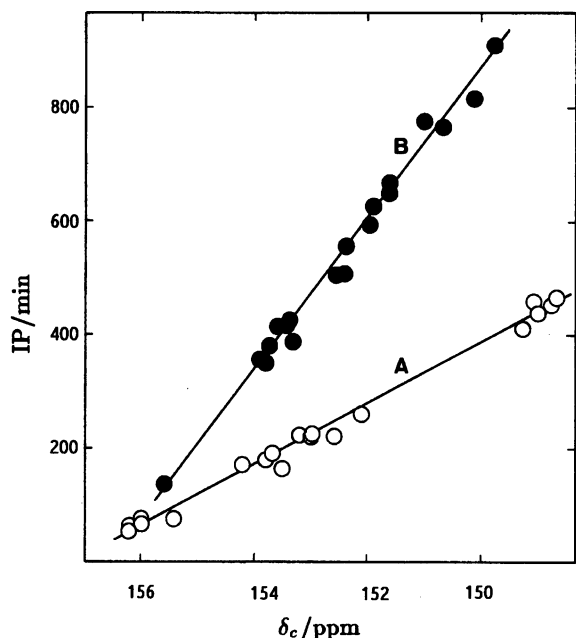
Fig. 1.   Plots of the IP values vs. ^{13}C shifts of the ipso-carbon. Line A: Benzylphenols (○), corr. coeff.= 0.994 and B: Bisphenols (●), corr. coeff.=0.991.

Experimental

Determination of Antioxidant Activity.   Measurements of the oxygen-absorption rates were performed with an isobaric gas absorption apparatus under a closed-flow system (2.0±0.1L oxygen h^{-1}) provided with an electrolyser using 50 cm^3 of tetralin containing antioxidant (0.001 mol dm^{-3}) and azobis(isobutyronitrile) as the initiator (0.01 mol dm^{-3}). The oxidation temperature was kept at 60±0.1°C and oxygen absorption was periodically measured in a constant-pressure closed system. The IP/min value was determined in the usual way.[4]

Computation

Ab initio molecular orbital calculations were carried out for the reactions, Eqs. 1—14a (see Scheme 1), with the GAUSSIAN 80 programs.[5] The geometries for all of the structures were optimized at the HF level with the STO-3G basis set[6] by using the energy gradient method.[7] The energies and structures of the transition states were also calculated in the same way as that mentioned above; the aromatic ring involved in the reactions, however, was only fixed with that of optimized phenol geometry. The ΔH and E_a values were obtained from the total energies for the optimum structures of both systems and the energy of the transition state (E_{ts}), as follows:

$$\Delta H(\text{kJ mol}^{-1}) = -2625.460[E_{\text{total}}(\text{reactants})$$
$$-E_{\text{total}}(\text{products})] \qquad (I)$$

$$E_a(\text{kJ mol}^{-1}) = -2625.460[E_{\text{total}}(\text{reactants}) - E_{ts}]$$

$$1 \text{ A.U.} = 2625.460 \text{ kJ mol}^{-1} \qquad (II)$$

The dissociation energies of the O–H bond in all of the reactions were obtained from three total energies, as follows: $D(\text{O–H})$ (kJ mol^{-1})$=-2625.460(E-E_R-E_H)$, where E denotes the total energy of phenol derivative, E_R is the total energy of phenoxyl radical, and E_H is the total energy of hydrogen radical produced by the abstraction. The obtained values are shown in Tables 1, 2, and 3.

Results and Discussion

Correlations between the ΔH and E_a Values, the E_a and $D(\text{O–H})$ Values, and the ΔH and $D(\text{O–H})$ Values.   In order to understand the factors affecting hydrogen abstraction in the chain-breaking reaction (Eqs. 1—14), several attempts were made to plot the activation parameters, ΔH, E_a, and $D(\text{O–H})$ values, listed in Table 1. From the calculated ΔH values, hydrogen abstraction proved to be an endothermic reaction. An approximately linear relationship between the ΔH and E_a values is shown in Fig. 2. The E_a values increased with the ΔH values, and the slope value $(\Delta E_a/\Delta(\Delta H))$ is 0.40, except for the value in Eq. 3. This fact indicates that hydrogen abstraction in the chain-breaking reaction follows the Evans–Polanyi rule.[11]

Subsequently, a linear relation of the E_a with the $D(\text{O–H})$ values and further excellent correlation of the ΔH with the $D(\text{O–H})$ values were obtained, as can be seen in Fig. 3.

It can thus be concluded that the activation parameters have very good relationships between the ΔH and E_a values, the E_a and $D(\text{O–H})$ values, and the ΔH and $D(\text{O–H})$ values.

Substituent Effect of Phenolic Antioxidant.
This problem will now be discussed from the standpoint of the activation parameters on the basis of hydrogen abstraction from the OH substituent of phenols by the
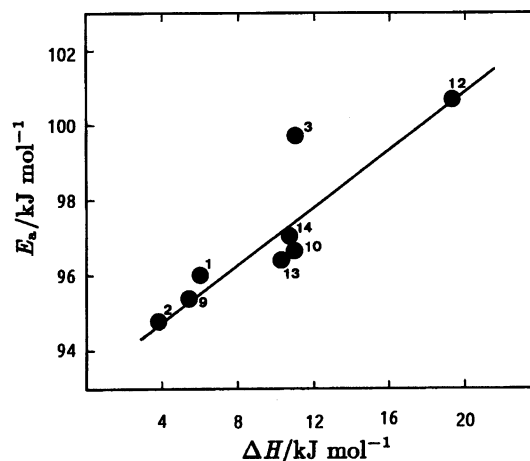

Fig. 2.   Plots of ΔH vs. E_a values, corr. coeff.=0.9723, except for that in Eq. 3.

Table 1. Activation Parameters with Activities as Phenolic Antioxidants

Eq.	R	ΔH/kJ mol^{-1}	E_a/kJ mol^{-1}	D(O–H)/kJ mol^{-1}	IP/min[a]	IP/min[b]	IP/h[c]	IP/h[d]	δ_c/ppm[e]
1	H	6.02	96.02	273.09	60	23	1.5	1.7	156.4
2	o-CH$_3$	3.81	94.81	270.91	120	86			155.4
3	o-NH$_2$	10.96	99.79	281.88	735				144.9
4	o-OH	8.24		275.27	1890	472	5.5	5.1	145.6
5	m-CH$_3$	9.83		276.90	90	40	—	—	157.4
6	m-NH$_2$	15.98		283.05	225		2.5		158.9
7	m-OH	16.11		283.21	135	53	1.5	1.8	159.0
8	m-F	10.54		277.61					
9	p-CH$_3$	5.48	95.44	272.55	165	121			154.1
10	p-NH$_2$	11.05	96.69	278.11	1470	551			144.4
11	p-OH	8.28		275.35	135	234	2.0	3.5	150.8
12	p-OCH$_3$	19.46	100.71	286.52		202			151.4
13	p-F	10.29	96.44	277.36	—	58	—	—	
14	p-Cl	10.75	97.03	277.82	—	34	—	—	157.0

a) The data in Ref. 8 (0.00005 mole antioxidant in 100 g of gasoline). b) This work (tetralin), except of the values in R=H, p-CH$_3$, and p-NH$_2$, from Ref. 1. c) The data in Ref. 9 (0.01 wt% of antioxidant in paraffin wax). d) The data in Ref. 10 (0.001 mole of antioxidant in 1 kg of paraffin wax). e) C-13 chemical shifts were observed as a 1 mmol cm^{-3} solution in (CD$_3$)$_2$CO.

Table 2. Electron Densities of the Oxygen and ipso-Carbon Atoms of the OH Substituents of p-Substituted Phenols, in the Reactants, Transition, and Products States

Eq.	R	X	Oxygen Reactants	Oxygen Transition	Oxygen Products	ipso-Carbon Reactants	ipso-Carbon Transition	ipso-Carbon Products
1	H	OOH	8.275484	8.172075	8.086672	5.876160	5.910279	5.907503
1a	H	OOCH$_3$	8.275484	8.172872	8.086672	5.876160	5.910380	5.907503
9	CH$_3$	OOH	8.276223	8.172809	8.095970	5.880468	5.912314	5.926302
10	NH$_2$	OOH	8.276878	8.172258	8.090684	5.890620	5.915415	5.929505
10a	NH$_2$	OOCH$_3$	8.276878	8.209877	8.090684	5.890620	5.902264	5.929505
12	OCH$_3$	OOH	8.276438	8.170878	8.089541	5.889672	5.911332	5.929291
12a	OCH$_3$	OOCH$_3$	8.276438	8.172040	8.089541	5.889672	5.911402	5.929291
13	F	OOH	8.274458	8.169826		5.883228	5.911941	5.926467
14	Cl	OOH	8.270464	8.165181	8.081646	5.869045	5.905604	5.920882
14a	Cl	OOCH$_3$	8.270464	8.166342	8.081646	5.869045	5.905661	5.920882

Table 3. Values Condensed to Atoms and Bonds (All Electrons)

Eq.	R	State	ipso-Carbon	C–O Bond	Oxygen	O–H Bond	Hydrogen
1	H	Reactants	4.753150	0.289659	7.770440	0.258173	0.592409
		Transition	4.828986	0.263831	7.858188	0.100605	0.636617
		Products	4.856235	0.252917	7.870986		
2	o-CH$_3$	Reactants	4.774215	0.289406	7.775968	0.258271	0.59356
		Transition	4.863936	0.258738	7.870633	0.100347	0.636959
		Products	4.880814	0.247944	7.883925		
9	p-CH$_3$	Reactants	4.757283	0.289052	7.771696	0.257985	0.593621
		Transition	4.830774	0.263646	7.858612	0.100873	0.636760
		Products	4.868226	0.248083	7.880854		
10	p-NH$_2$	Reactants	4.767250	0.287356	7.773929	0.257707	0.595476
		Transition	4.832871	0.263173	7.858427	0.100745	0.636742
		Products	4.859541	0.252321	7.871951		
12	p-OCH$_3$	Reactants	4.766084	0.287643	7.773004	0.257897	0.594411
		Transition	4.830025	0.263725	7.857170	0.100194	0.636684
		Products	4.858267	0.252474	7.870564		
14	p-Cl	Reactants	4.745546	0.291283	7.762915	0.259028	0.585613
		Transition	4.823718	0.264345	7.852934	0.098053	0.636272
		Products	4.850560	0.253290	7.862102		

peroxyl radical (see Structure I in Chart 1). The parameters are shown in Table 1 along with the IP values determined under various conditions.
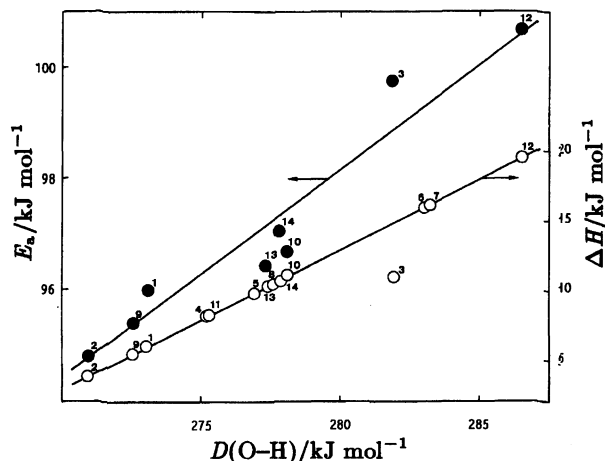
In the cases of o- and p-cresols (Eqs. 2 and 9), the E_a

Fig. 3. Plots of D(O–H) vs. E_a values (•), corr. coeff.$=0.9744$, and of D(O–H) vs. ΔH values (○), corr. coeff.$=0.9999$, except for those in Eq. 3.

values decrease by 1.21 and 0.58 kJ mol^{-1}, compared with that of phenol (Eq. 1, R=H), respectively. Similarly, the ΔH values decrease by 2.21 and 0.54 kJ mol^{-1}, respectively. In the cases of p-fluoro- and p-chlorophenols (Eqs. 13 and 14), the ΔH and E_a values increase compared with those of phenol. These facts indicate that the electron-releasing substituent, like the o- and p-CH$_3$ substituents, decreases the ΔH and E_a values and increases antioxidant activities (see IP values in Table 1), whereas the electron-attracting substituent, like the p-F and p-Cl substituents, increases the transition energy barrier, and decreases the activity. Thus, p-fluoro- and p-chlorophenols show a very poor antioxidant activity.

Though the o- and p-NH$_2$ substituents in phenol have a strong electron-releasing effect, the ΔH and E_a values increase by 4.94 and 5.03 kJ mol^{-1} for ΔH and by 3.77 and 0.67 kJ mol^{-1} for E_a, respectively, compared with those of phenol (see Eqs. 3 and 10). A similar result was shown by the ΔH values in the cases of the o- and p-OH substituents (Eqs. 4 and 11). On the other hand, these phenols all have excellent antioxidant activities, by the use of gasoline,[8] tetralin,[1] and paraffin wax[9,10] as substrates, as can be seen in Table 1.

A description of the above-mentioned facts is as follows. According to a proposal by Scott,[12] substituents that delocalize electrons in the arylaminyl or aryloxyl radicals increase antioxidant activity. In the transition state (see Chart 1), there is both partial separation of charge between the alkylperoxyl and the aromatic ring as well as partial delocalization of the electron in the π-bond system. It can therefore be considered that the substituents like NH$_2$ and OH in the o- or p-position in phenol, which release electrons or delocalize unpaired electrons decrease the transition state energy involved in hydrogen abstraction. From the data, ΔH, D(O–H), and IP values in Table 1, it was also recognized that the abilities of delocalization of both meta-substituents

(Eqs. 6 and 7) are inferior to those of the o- or p-positions (Eqs. 3, 4, 10, and 11).

Variation of Electron Densities of the Oxygen and ipso-Carbon Atoms of the OH Substituents in p-Substituted Phenols. From our study on p-substituted benzene and benzylbenzene systems by using ^{13}C NMR and a dual substituent parameter method,[13] it was found that electron transmission through the ipso-carbon to the oxygen in p-substituted phenols may be increased by increasing the electron density of the ipso-carbon. However, it is not clear how to estimate to what extent electrons move between the two atoms and how they take part in the reaction steps. In this work, data concerning the electron densities of the two atoms were obtained, as can be seen in Table 2. Consequently, variations of the electron densities through the reaction states, namely, the reactants, transition, and products states, were recognized. The electron densities on the oxygen atoms decreased linearly through the reaction states in the range of 8.27— 8.28 to 8.08—8.10, whereas those on the ipso-carbons gradually increased in the range of 5.87—5.89 to 5.92— 5.93, except for the value in the product state of Eq. 1.

These data make it possible to determine to what extent electron densities may be decreased or increased through reactions. We then obtained the values of the differences in the electron densities between the reactants and the transition states. Attempts were made to plot their differences for the oxygen and ipso-carbon atoms against the ΔH and E_a values, respectively. Figure 4 shows that the ΔH and E_a values decrease linearly by a decreased difference in the electron density of the oxygen atom, except for the values in Eqs. 12 and 12a. In the case of the halogen substituents, the E_a values bear another linear relationship. On the contrary, in the case of the ipso-carbon, the ΔH and E_a values de-
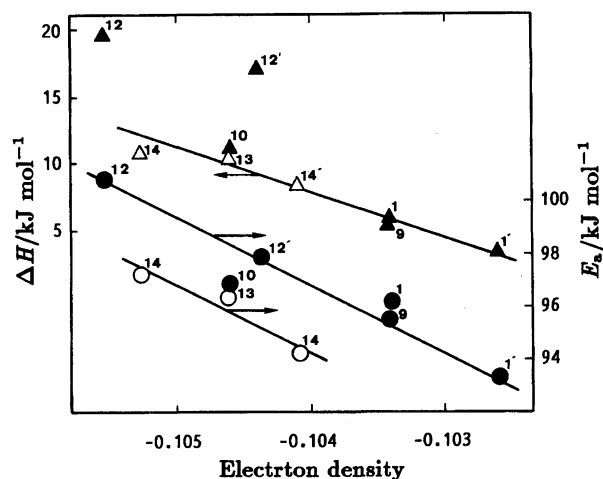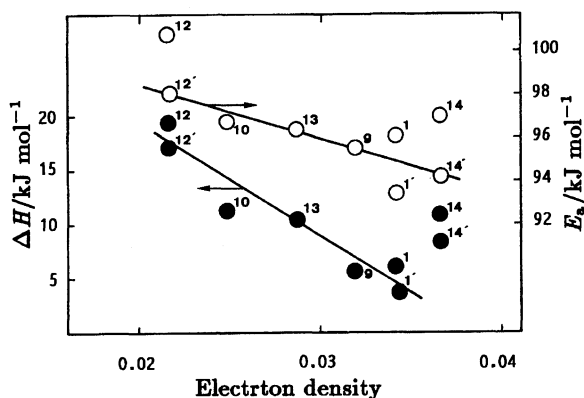

Fig. 4. Plots of ΔH (▲) or E_a (•) values vs. differences in the electron densities of the oxygen atoms, [(Transition) − (Reactants)] states. △ and ○: a phenol having a halogen substituent.

crease by an increased difference in the electron density, except for a few values, as can be seen in Fig. 5.

The above results also support the idea that in the transition state, the electron density of the oxygen decreases, since the electrons move toward the new bond formed with the peroxyl radical (see Structure I in Chart 1), whereas the density of the ipso-carbon increase mostly by a resonance contribution of the p-substituent.

Variation of the Electron Density in the Reaction. Various distributions of the electron densities may arise in three reaction states on the atoms and

Fig. 5. Plots of ΔH (•) or E_a (o) values vs. differences in the electron densities of the ipso-carbon atoms, [(Transition) − (Reactants)] states.
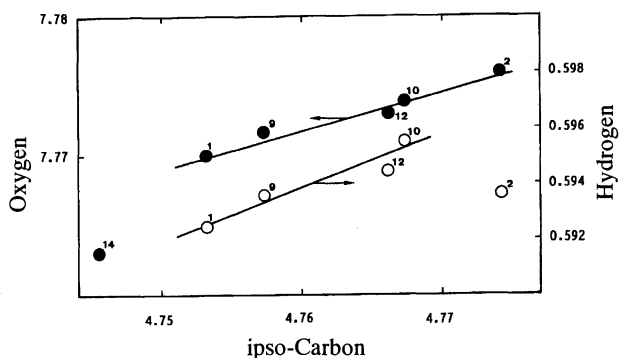

Fig. 6. Relationships in the electron densities between the ipso-carbon and oxygen atoms (•) and between the ipso-carbon and hydrogen atoms (o), in the reactants state.

Table 4. Differences in Electron Densities Condensed to Atoms and Bonds; [(Transition)−(Reactants)]×10²

Eq.	R	ipso-Carbon	C-O Bond	Oxygen	O-H Bond	Hydrogen
1	H	7.58	−2.58	8.77	−1.58	4.42
2	o-CH₃	8.97	−3.07	9.47	−1.58	4.34
9	p-CH₃	7.35	−2.54	8.69	−1.58	4.31
10	p-NH₂	6.57	−2.41	8.45	−1.57	4.13
12	p-OCH₃	6.39	−2.39	8.42	−1.58	4.22
14	p-Cl	7.82	−2.69	9.00	−1.61	5.07

bonds in the reaction of phenols. The calculated values of the electron densities on the ipso-carbons, oxygens, and hydrogens and those on the C-O and O-H bonds are shown in Table 3.

The values of the ipso-carbon and oxygen atoms increase through a reaction from the reactants to the product state. The values of the hydrogens increase toward the transition state and those from 0.636 to 0.637 are almost equal to the mean value, 0.6367. On the contrary, the values of the C-O and O-H bonds decrease through the reaction.

From these data, linear relationships of the electron densities between the ipso-carbons and oxygens and between the ipso-carbons and hydrogens in the reactants states are shown in Fig. 6. In this state, the electron densities of the oxygen and hydrogen increase with an increase of that of the ipso-carbon.
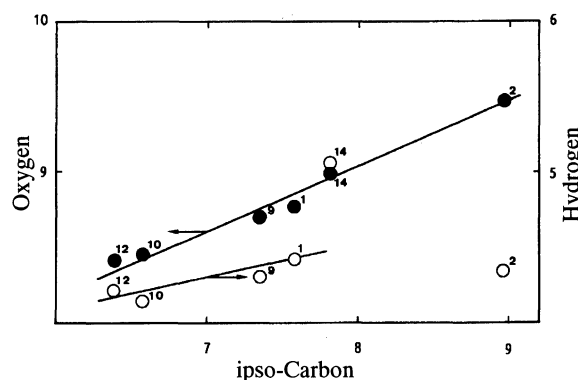

Fig. 7. Relationships of the differences in the electron densities, [(Transition) − (Reactants)]×10², between the ipso-carbon and oxygen atoms (•) and between the ipso-carbon and hydrogen atoms (o).
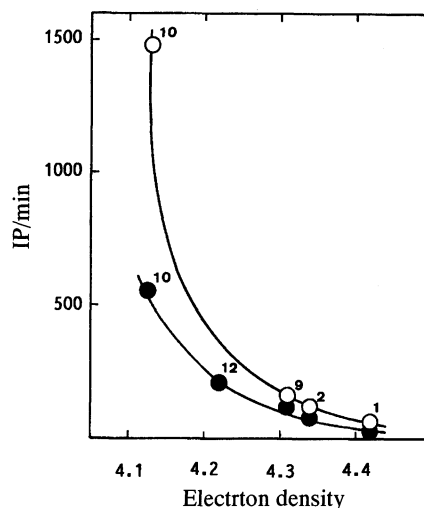

Fig. 8. Relations between the IP values and differences in the electron densities of the hydrogen atoms, [(Transition) − (Reactants)]×10², •: IP from Ref. 1 and this work; o: IP from Ref. 8.

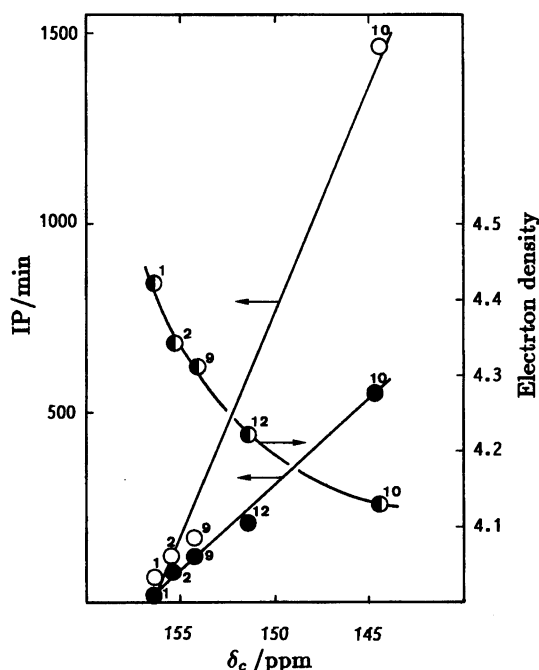Fig. 9.   Relations between ^{13}C shifts of the ipso-car-
bons and IP values, ●: from Ref. 1 and this work; o:
from Ref. 8, and between ^{13}C shifts of the ipso-car-
bons and differences in the electron densities of the
hydrogen atoms, (◐).

Subsequently, it is necessary to determine the varia-
tion of the electron density between the transition and
reactants states. These differences in the electron den-
sities are shown in Table 4. Linear relationships in the
differences between the ipso-carbon and oxygen atoms
and between the ipso-carbon and hydrogen atoms are
shown in Fig. 7. The differences in the electron densi-
ties for the oxygen and hydrogen atoms increase due to
an increase in those for the ipso-carbons, except for the
values in Eqs. 2 and 14.

The above-mentioned results indicate that the elec-
tron density increased may be regarded as being a sta-
bilization of the transition state for the abstraction of a
hydrogen. This hydrogen requires a certain number of
electrons for its reaction. This amount, around 0.6367,
was obtained from the data in Table 3, as was that
mentioned above. Consequently, each hydrogen needs
to supply the corresponding electron; these values can
be found in Table 4. When the reaction proceeds to
the transition state by supplying a minimized number
of electrons, it takes place easily with a lessened acti-
vation barrier. In the relation between the ipso-carbon
and hydrogen atoms, the order of the tendency increas-

ing in the electron density is $1<9<12<10$ in Fig. 6; that
in the difference, however is $10<12<9<1$ in Fig. 7. It
was reasonable to obtain the reverse direction to each
other in both orders.

On the basis of the results, we tried to attain relations
between the calculated and experimental data. From
the view points mentioned in this introduction, the re-
lations between the differences in the electron densities
of the hydrogens (Table 4) and two kinds of IP values
(Table 1) were obtained. As can be seen in Fig. 8, the
IP values decreased with an increase in the differences.
From the standpoint of the ipso-carbon chemical shift,
Fig. 9 shows the relations between the shifts and two
kinds of IP values, and the differences in the electron
densities. Both figures indicate that a suitable number
of electrons must be supplied through the ipso-carbon
to the hydrogen in the transition state until it reaches
the constant value required to carry out hydrogen ab-
straction. Therefore, the ^{13}C chemical shift of the ipso-
carbon may be considered as being a suitable, objective,
and reliable indication of the antioxidant activity.

References

1)   K. Tanaka, S. Sakai, S. Tomiyama, T. Nishiyama, and
F. Yamada, Bull. Chem. Soc. Jpn., 64, 2677 (1991).
2)   J. L. Bolland and P. Ten Have, Discuss. Faraday Soc.,
2, 252 (1947); Trans. Faraday Soc., 43, 201 (1947).
3)   F. Yamada, T. Nishiyama, Y. Suzuura, and T.
Yamamura, Bull. Chem. Soc. Jpn., 58, 115 (1985).
4)   F. Yamada, T. Nishiyama, M. Yamamoto, and K.
Tanaka, Bull. Chem. Soc. Jpn., 62, 3603 (1989).
5)   J. S. Binkley, R. A. Whiteside, R. Krishnan, R.
Seeger, D. J. DeFrees, H. B. Schlegel, S. Topiol, L. R.
Kahn, and J. A. Pople, "GAUSSIAN 80," Carnegie Mellon
University, Pittsburg, PA (1980).
6)   W. J. Hehre, R. F. Stewart, and J. A. Pople, J. Chem.
Phys., 51, 2657 (1969).
7)   A. Komornicki, K. Ichida, K. Morokuma, R.
Ditchfield, and M. Conrad, Chem. Phys. Lett., 45, 595
(1977).
8)   C. D. Lowry, G. Egloff, J. C. Morrell, and C. G.
Dryer, Ind. Eng. Chem., 25, 804 (1933).
9)   S. Matsuda and F. Yamada, Kogyo Kagaku Zasshi,
60, 566 (1957).
10)   F. Yamada, T. Nishiyama, and Y. Nakai, J. Am. Oil
Chem. Soc., 60, 1651 (1983).
11)   M. G. Evans and M. Polanyi, Trans. Faraday Soc.,
31, 875 (1935).
12)   G. Scott, Bull. Chem. Soc. Jpn., 61, 165 (1988).
13)   Y. Nakai, T. Takabayashi, and F. Yamada, Org.
Magn. Reson., 13, 94 (1980).