January, 1993] © *1993 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, ***66***, *269—274(1993)*

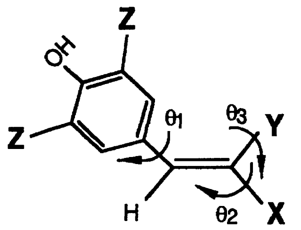
Acidity and Dynamic Structure of the Potent Uncoupler SF6847 (2,6-Di-*t*-butyl-4-(2,2-dicyanovinyl)phenol) and Its Derivatives

Hideto MIYOSHI,* Ze-jian GUO,† Toshio FUJITA,†† and Hajime IWAMURA
Department of Agricultural Chemistry, Kyoto University, Kyoto 606

(Received August 24, 1992)

The acid dissociation constant (K_a) of a series of 2,6-di-*t*-butyl-4-(disubstituted vinyl)phenols was measured in water spectrophotometrically at 25°C. The electronic substituent effects of the substituted vinyl moiety on the pK_a value were examined by dual-electronic-parameter analyses. The electronic effects of the two substituents at the end of the vinyl moiety were found to be not equal in the acid-base dissociation equilibrium. The inductive and resonance effects of the X-substituents *trans* to the benzene ring and the inductive effect of the Y-substituents *cis* to the benzene ring were significant factors governing the pK_a value. These results and the molecular orbital calculation studies suggest that although the π-bonded X-substituents are coplanar to the vinyl plane, the π-bonded Y-substituent are twisted by a steric repulsion with the benzene ring. The variations in the pK_a value of variously substituted analogs were related with the ease of intramolecular rotational motion around the bond connecting the vinyl group and the benzene ring, based on ^{1}H NMR studies.

2,6-Disubstituted-4-(2,2-disubstituted vinyl)phenols (Fig. 1), such as SF6847(Fig. 1; compound **9**) and its analogs, exhibit potent uncoupling activity with energy-transducing biomembranes, such as rat-liver mitochondria and spinach chloroplasts.[1,2] The acid dissociation constant (K_a) of these compounds is one of the important factors which determine the uncoupling potency.[3] SF6847 (**9**) and its analogs have two conspicuous structural characteristics which should govern their pK_a value. One is that the acidic group (phenolic OH) is highly hindered by the 2,6-disubstitution; other is the dynamic rotational motion around the C–C bond between the benzene ring and the vinyl moiety.



1: X = Y = COOEt, Z = *t*-Bu
2: X = COOEt, Y = CN, Z = *t*-Bu
3: X = CN, Y = H, Z = *t*-Bu
4: X = CONH2, Y = CN, Z = *t*-Bu
5: X = COMe, Y = COOEt, Z = *t*-Bu
6: X = SO2Me, Y = CN, Z = *t*-Bu
7: X = COOEt, Y = H, Z = *t*-Bu
8: X = COOMe, Y = CN, Z = *t*-Bu
9: X = Y = CN, Z = *t*-Bu
10: X = COOH, Y = Me, Z = *t*-Bu
11: X = COOH, Y = H, Z = *t*-Bu
12: X = Cl, Y = H, Z = *t*-Bu

Fig. 1. General structure of the compounds studied. The X- and Y-substisuents are *trans* and *cis* to the benzene ring, respectively. The molecular orbital calculation was performed with regard to changes in the θ_1, θ_2, and θ_3 angles (see text).

The effect of 2,6-di-*t*-butyl substituents upon the thermodynamic and spectroscopic properties in water have been investigated for such compounds as 2,6-di-*t*-butylphenol[4,5] and 2,6-di-*t*-butylpyridine.[6,7] These compounds exhibit anomalous acid-base dissociation behaviors compared with that of 2,6-disubstituted compounds with less congested alkyl groups. The anomalous behaviors are postulated to be due to a steric inhibition of solvation of the dissociation group, and a loss of entropy due to the restricted internal rotation of the *t*-butyl groups caused by steric interactions in the hydrated ionized species.[7]

Yoshikawa et al.[8,9] have examined the dynamic structure of SF6847 (**9**) and its derivatives (Fig. 1; X=Y=CN, Z=H, Me, Et, *i*-Pr, *s*-Bu, or *t*-Bu) by ^{1}H NMR spectroscopic and molecular orbital studies. The variations in the pK_a value of these SF6847 analogs are explained in terms of the intramolecular rotation around the C–C bond between the benzene ring and the vinyl moiety. In their studies, however, the substituents on the vinyl moiety are limited to the dicyano group.

In this study we measured the pK_a values of a series of 2,6-di-*t*-butyl-4-(2,2-disubstituted vinyl)phenols (Fig. 1; Z=*t*-Bu), and examined the electronic effects of substituents at the vinyl moiety on the pK_a value by dual-electronic-parameter analysis[10] and NMR spectroscopic studies. The electronic effects of the two substituents at the vinyl moiety were not identical in governing the acid-base dissociation equilibrium. The variation in the pK_a value was linearly correlated with the intramolecular rotational mobility of the anionic form around the C–C bond between the benzene ring and the vinyl moiety.

---

† Present address: The Suntory Institute for Bioorganic Research, Osaka 618.

†† Present address: Fujitsu Kansai Systems Laboratory, Osaka 540.

Experimental

Compounds **1**—**9** in Table 1 were the same samples as those used previously.[1)] Compounds **10** and **11** were generous gifts from Dr. K. Watanabe of the Kanegafuchi Chemical Co.[11)] Compound **12** was prepared from **11** with *N*-chlorosuccinimide.[12)] Calcd for $C_{16}H_{23}O_1Cl_1$: C, 72.08; H, 8.63; Cl, 13.29%. Found; C, 72.15; H, 8.55; Cl, 13.30%. ^{1}H NMR ($CDCl_3$) δ=1.50 (9H, s, *t*-Bu), 6.45 (1H, d, J=15.1 Hz), 6.77 (1H, d, J=15.1 Hz), and 7.13 (2H, s, aromatic protons).

The pK_a values of compounds **1**—**9** in water (25°C) were taken from a previous paper.[1)] For compounds **10**—**12**, the pK_a value was measured spectrophotometrically (25°C) as reported.[1)]

^{1}H NMR spectra were measured at 400 MHz with a JEOL GSX-400 NMR spectrometer. For measuring the NMR spectra of anionic forms of SF6847 analogs, methamol-d_4 containing 0.1 mol dm^{-3} sodium hydroxide was used. Variable-temperature studies were carried out using the standard temperature-regulation apparatus of the spectrometer. The ^{13}C NMR spectra were recorded on a General Electronics GN-300 spectrometer at resonance frequencies of 75 MHz.

Molecular orbital calculations were carried out using the AMPAC program (QCPE No. 523) with AM1 parameterization[13)] running on a FACOM M-382 computer. The starting coordinates were obtained from ANCHOR (Kureha Chemical Industry Co., Ltd. and Fujitsu Ltd., Tokyo, Japan), a program system for molecular modeling. The minimum energy conformation was fully optimized with the precise option. In each calculation, all of the bond lengths, bond angles, and dihedral angles were allowed to vary while the energy was minimized.

Results

Regression Analyses of Electronic Substituent Effects. The pK_a values of compounds **10**—**12** were newly measured and are listed in Table 1 together with those of the other compounds cited from a previous study.[1)] The variation in the pK_a values was large in spite of the site of the substituents being quite distant from the dissociation group. We sought to correlate the pK_a values of the SF6847 analogs by applying an extended Hammett-Taft-type equation (dual-electronic-parameter equation[10)]) and a correlation analysis.

First the pK_a value was correlated with the simple sum of σ_I and (inductive effect parameter) and σ_R (resonance effect parameter), or σ_I and σ_{R^-} (through-resonance effect parameter) of the X- and Y-substituents, as follows:

$$\begin{aligned} pK_a = &-3.431\Sigma\sigma_I - 5.365\Sigma\sigma_R + 11.865 \\ &\quad(0.750) \qquad (2.406) \qquad (0.595) \\ &(n=12, s=0.484, r=0.972) \end{aligned} \tag{1}$$

$$\begin{aligned} pK_a = &-2.802\Sigma\sigma_I - 2.916\Sigma\sigma_{R^-} + 11.924 \\ &\quad(0.948) \qquad (1.514) \qquad (0.680) \\ &(n=12, s=0.537, r=0.966) \end{aligned} \tag{2}$$

In these and the following equations, n is the number of compounds, s the standard deviation, and r the correlation coefficient. The figures in parentheses are the 95% confidence interval. In both equations, each term was justified at a level higher than 99.9%. The use of a combination of $\Sigma\sigma_I$ and $\Sigma\sigma_{R^-}$ values gave a slightly poorer correlation than that of the $\Sigma\sigma_I$ and $\Sigma\sigma_R$ values, indicating that the delocalization of a negative charge of the phenolate anion due to a through-resonance effect is not a significant factor regarding the acid dissociation behavior. Combining the electronic effects of the X- and Y-substituents did not produce any good correlations.

To try to improve the correlation, we separated the electronic effects of the X- and Y-substituents from each other based on the assumption that the bulkier substituent is *trans* (X) to the benzene ring and the smaller one is *cis* (Y). This assumption concerning the geometrical isomerism could be reasonable, since an aldol-type condensation reaction, by which all test compounds, except for **12**, has been synthesized, generally gives the *E* form.[14)] Compound **12** was shown to be the *E* form from the ^{1}H NMR spectra ($^3J_{HH}$=15 Hz).[15)] To verify our assumption, the configuration of the compounds was examined using the long-range ^{13}C–H coupling experiments[16)] while taking compounds **4** and **5** as examples. For compound **4**, the $^3J_{CH}$ value between the cyano carbon and vinyl proton was 13.2, while the value between the carbonyl carbon and the vinyl proton was 5.7 Hz. The $^3J_{CH}$ values between the carbonyl carbon and the vinyl proton, for the ethoxy carbonyl and acetyl groups, were 12.5 and 7.0 Hz, respectively, for compound **5**. These observation demonstrated that the amide group in **4** and the acetyl group in **5** are *trans* to the benzene ring.[16)]

On the basis of the configuration described above, the following equation was derived as being the equation of best quality:

$$\begin{aligned} pK_a = &-2.702\sigma_I(X) - 4.650\sigma_R(X) - 5.392\sigma_I(Y) + 11.918 \\ &\quad(0.818) \qquad (1.480) \qquad (0.668) \qquad (0.325) \\ &(n=12, s=0.205, r=0.996) \end{aligned} \tag{3}$$

The correlation was highly improved from Eqs. 1 and 2. Each of the terms is significant at a level higher than 99.9%. Although the colinearity between σ_I(Y) and σ_R(Y) is somewhat high (r=0.731), the addition of the σ_R(Y) term to Eq. 3 was not justified at over the 90% level. This result indicates that the resonance effect of the Y-substituent does not play any significant role in the acid-dissociation behavior. This may be attributed to the supposition that π-bonded Y-substituents are twisted from the vinyl plane due to a steric repulsion between the Y-substituents and the benzene ring. Moreover, the use of the σ_{R^-}(X) term in place of the σ_R(X) term did not improve the correlation, indicating that the through-resonance effect between the negatively charged center of the anionic form and the X-substituent is not an important factor governing acid

Table 1. pK_a and Electronic Substituent Constants of Test Compounds

Compd No.	pK_a Obsd[a]	Calcd[b]	Dev.	$\sigma_I(X)$[c]	$\sigma_I(Y)$[c]	$\sigma_R(X)$[c]	$\sigma_R(Y)$[c]	$\sigma_{R^-}(X)$[c]	$\sigma_{R^-}(Y)$[c]
1	9.29	8.98	0.31	0.30	0.30	0.11	0.11	0.31	0.31
2	7.51	7.52	−0.01	0.30	0.57	0.11	0.08	0.31	0.26
3	9.75	10.01	−0.27	0.57	0	0.08	0	0.26	0
4	7.73	7.72	0.01	0.28	0.57	0.08	0.08	0.23	0.26
5	8.67	8.56	0.11	0.30	0.30	0.20	0.11	0.41	0.31
6	6.77	6.74	0.03	0.59	0.57	0.11	0.08	0.35	0.26
7	10.82	10.60	0.22	0.30	0	0.11	0	0.31	0
8	7.45	7.61	−0.16	0.32	0.57	0.08	0.11	0.30	0.26
9	6.84	6.93	−0.09	0.57	0.57	0.08	0.08	0.26	0.26
10	11.50[d]	11.42	0.08	−0.19	−0.01	0.23	−0.16	0.31	−0.16
11	11.10[d]	11.36	−0.26	−0.19	0	0.23	0	0.31	0
12	11.82[d]	11.81	0.01	0.47	0	−0.25	0	−0.30	0

a) Unless otherwise noted, from Ref. 1. b) By Eq. 3. c) From Ref. 10. d) Newly measured.

dissociation.

To verify the constant term of Eq. 3, the following analyses were performed. Cohen and Jones[4] studied the substituent effects on the pK_a value in water for a series of 2,6-di-*t*-butyl-4-substituted phenols. The substituents at the 4-position (para to hydroxyl group) were simple ones, as listed in Table 2. They showed a linear dependence of the pK_a values on the σ_{para^-} constant of the substituents. The pK_a and σ_{para^-} values for 12 compounds are listed in Table 2. We examined the relationship between pK_a and σ_{para^-} by regression analysis and derived Eq. 4.

$$\begin{aligned} \mathrm{p}K_a &= -3.227\sigma_{\text{para}^-} + 11.593 \qquad (4) \\ &\quad\;\; (0.123) \qquad\quad (0.071) \\ &\quad (n = 12, s = 0.085, r = 0.999) \end{aligned}$$

The constant term of Eq. 4 was almost identical to the pK_a value of 2,6-di-*t*-butylphenol (being 11.70[4]), thus verifing Eq. 4. The pK_a value of unsubstituted derivatives (Fig. 1; X=Y=H, Z=*t*-Bu) was estimated by Eq. 4 using σ_{para^-} ($CH=CH_2$)=−0.08.[17] The estimated value is 11.85, corresponding very well to the constant value (11.92) of Eq. 3. This result established the validity of Eq. 3 for the variation of the pK_a values.

Conformational Studies by Molecular Orbital Calculations. To obtain information concerning the dynamic structure we performed semiempirical molecular orbital (MO) studies on the conformation of the compounds. Changes in the total energy with angle θ_1 (in Fig. 1, θ_1 is 0° and 90° when the vinyl plane is coplanar and perpendicular to the benzene ring plane, respectively) for the neutral and anionic forms of compound **9** are shown in Fig. 2. MO studies showed that the rotational barrier at $\theta_1=90°$ is not large and that the minimum energy is found at about $\theta_1=40°$ for the neutral form. Contrarily to the neutral form, the "planar structure" ($\theta_1=0°$) was the most stable conformation for the anionic form, and the energy barrier at $\theta_1=90°$ was very large. These results obtained for the anionic form differed from those of the MO calculations performed for the anionic form of 4-(2,2-dicyanovinyl)phenol (Fig. 1; X=Y=CN, Z=H) by Yoshikawa et al.[8] According to their study, the angular dependence of the total energies was essentially similar for both forms; that is, "planar structure" was quite unstable for both forms. Regarding the differences, a discuss will be presented later.

Table 2. pK_a Values of 2,6-Di-*t*-Butyl-4-Substituted Phenols and σ_{para^-} Constant

Substituent	pK_a Obsd[a]	Calcd[b]	Dev.	σ_{para^-}[c]
COO^-	10.80	10.82	−0.02	0.24[a]
SO_3^-	10.40	10.30	0.10	0.40[a]
COOEt	9.50	9.53	−0.03	0.64[d]
COMe	8.68	8.79	−0.11	0.87
CN	8.70	8.69	0.01	0.90
Me	12.23	12.14	0.09	−0.17
t-Bu	12.19	12.24	−0.05	−0.20
OMe	12.15	12.24	−0.09	−0.20
H	11.70	11.59	0.11	0
Br	10.83	10.85	−0.02	0.23
$CONH_2$	9.53	9.63	−0.10	0.61[d]
CHO	8.05	7.95	0.10	1.13

a) From Ref. 4. b) By Eq. 4. c) Unless otherwise noted, from T. Fujita and T. Nishioka, *Prog. Phys. Org. Chem.*, **12**, 49 (1976). d) From Ref. 17.

The angular dependence of the total energy was also studied concerning angles θ_2 and θ_3 (Fig. 1, θ_2, θ_3= 0° when the carbonyl plane is coplanar to the vinyl plane) of compounds **1** (X=Y=COOEt, Z=*t*-Bu) and **5** (X=COMe, Y=COOEt, Z=*t*-Bu). For the neutral and ionized forms of compound **1**, the minimum energy was found at $\theta_2=0°$ and $\theta_3=67°$, and $\theta_2=0°$ and $\theta_3=83°$, respectively. With compound **5**, the minimum energy was observed at $\theta_2=0°$ and $\theta_3=63°$, and $\theta_2=0°$ and $\theta_3=80°$ for the neutral and ionized forms, respectively. These results indicated that the carbonyl plane of the X-substituent is coplanar with the vinyl plane, and that

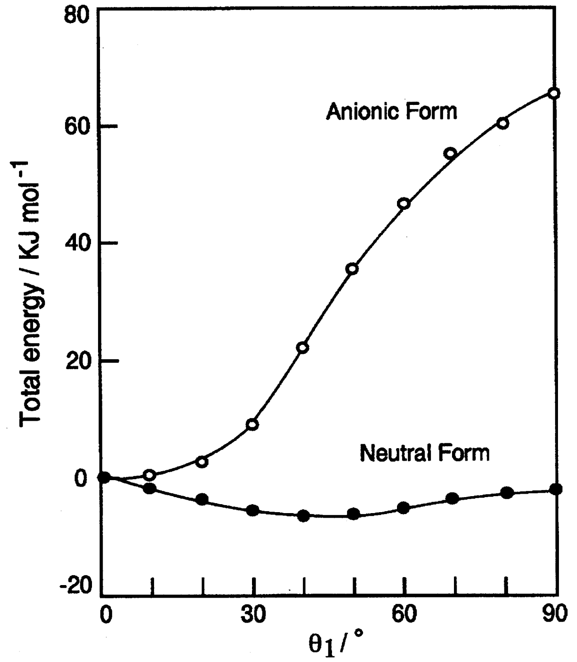


Fig. 2. Changes of the total energies with the angle θ_1 of compound **9** (see Fig. 1). The total energy of the planar structure (θ_1=0°) is standardized to zero.

of Y-substituent is twisted relative to the vinyl plane. It is suggested that the steric repulsion between the benzene ring and the carbonyl groups of the Y-substituent forces the carbonyl groups out of the plane of the vinyl bond.

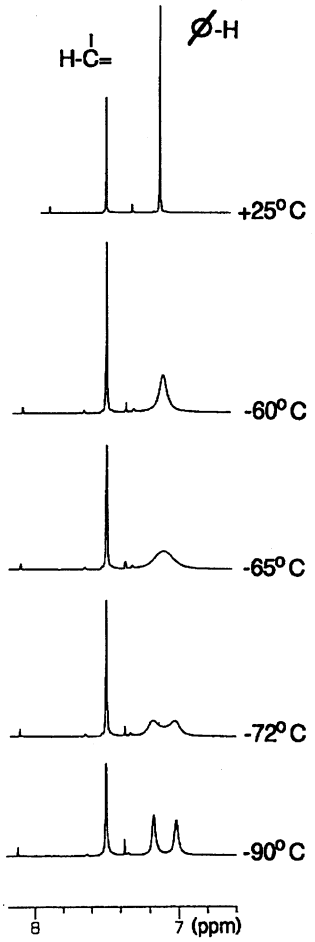


Fig. 3. 400 MHz ^{1}H NMR spectrum of the anionic form of compound **1** in methanol-d_4 containing 0.1 mol dm^{-3} sodium hydroxide.

Table 3. Activation Energies (E_A) of Intramolecular Rotation

Compound	$\Delta\nu$/Hz[a]	T_C/K[b]	E_A/kJ mol^{-1}[c]	pK_a
1	59	201±2	40.4±0.3	9.29
3	148	193±2	37.3±0.3	9.75
5	37	208±2	42.7±0.3	8.67
6	489	336±2	63.1±0.4	6.77
9	503	335±2	62.8±0.4	6.84

a) Chemical shift difference between the two aromatic protons at low temperature. b) Coalescence temperature. c) Calculated activation energies of intramolecular rotation (Refs. 18 and 19).

Conformational Studies by NMR Spectra. The temperature dependence of the ^{1}H NMR spectrum of the ionized form of compound **1** in methanol-d_4 containing 0.1 mol dm^{-3} NaOH is shown in Fig. 3. The two aromatic protons (meta to hydroxyl group) showed a single resonance down to −60° from 25°C. Upon a further lowering of the temperature, the signal broadened and split into the two signals at about −72°C (201 K). These results indicated that the frequency of the intramolecular rotation (or tumbling) of the vinyl moiety decreased with a decrease in the temperature, as reflected by the signal of the aromatic protons. The coalescence temperature of the signal of the aromatic protons was measured for the anionic form of five compounds, and is listed in Table 3 together with the chemical shift difference between the two aromatic protons. The activation energies of the rotational motion were calculated by a line-shape analysis[18,19] of the temperature dependence of the signal pattern of the aromatic protons. The activation energy in the anionic form of compound **9** (62.8 kJ mol^{-1}) is comparable to that reported by Yoshikawa et al. (64 kJ mol^{-1}).[8] It is of interest that the smaller are the pK_a values, the less mobile is the intramolecular rotation around the C–C bond between the benzene ring and the vinyl moiety. The relation between pK_a and the activation energy (E_A) of the rotation was formulated as follows:

$$\begin{aligned} \mathrm{p}K_\mathrm{a} &= -0.106E_\mathrm{A} + 13.470 \\ &\quad\ (0.029) \qquad (1.467) \\ &\quad\ (n=5, s=0.236, r=0.989) \end{aligned} \tag{5}$$

The aromatic protons of the neutral form of compounds **6** and **9** showed a singlet signal, even at −75°C in CDCl$_3$ (spectrum not shown). These results indicated that the vinyl moiety of the neutral form is much more mobile than that of the ionized form.

Discussion

Dual-electronic-parameter analyses of the pK_a values showed that the electronic effects of the X- and Y-substituents were not identical. The inductive and resonance effects of the X-substituents *trans* to the benzene ring and the inductive effect of the Y-substituents *cis* to the benzene ring were significant factors governing the pK_a value. The resonance effect of the Y-substituent was not significant. This result suggests that the carbonyl plane of the Y-substituents may not be coplanar to the vinyl plane, due to a steric repulsion by the benzene ring. This idea was supported by MO studies performed for compounds **1** and **5**. The use of σ_R-(X) in place of σ_R(X) in Eq. 3 did not improve the correlation, indicating that the through-resonance effect has very small contributions to acid dissociation, if any. This is probably due to the rather long distance between the dissociation group and the X-substituent.

The stability of the phenolate anion is governed by the electron-withdrawing ability of the vinyl moiety. When a negative charge of the phenolate anion is delocalized into the vinyl moiety, the C–C bond between the benzene ring and the vinyl moiety could be expected to have a somewhat double-bond character. Eq. 5 seems to support this argument. That is, the greater is the acid dissociation constant (K_a), the more is the rotational motion of the anionic form reduced, due to the formation of the double-bond character.

Yoshikawa et al.[8] performed MO calculations for 4-(2,2-dicyanovinyl)phenol (Fig. 1; X=Y=CN, Z=H) using the CNDO/2 program to obtain information concerning the dynamic structure of SF6847 analogs. The angular dependence of the rotational barrier in the neutral form reported by them was almost similar to that for compound **9** observed in the present study. However, the profile of energy changes with θ_1 in the anionic form was inconsistent with our results. They showed that the "planar structure" ($\theta_1=0°$) of the anionic form is quite unstable, that is, the planar structure is unstable by ca. 80 kJ mol^{-1}, compared to the conformation at $\theta_1=40°$. They also reported that the rotational barrier at $\theta_1=90°$ in the anionic form is slightly greater than that in the neutral form, the energy difference being within ca. 20 kJ mol^{-1}. Since we can not directly compare the results of our MO calculations for compound **9** with those by Yoshikawa at al.,[8] we performed MO calculations for both the neutral and the anionic forms of 4-(2,2-dicyanovinyl)phenol by the AM1 method. The calculation results were consistent with those for compound **9**. That is, the rotational barrier at $\theta_1=90°$ was not large, and the minimum energy was found at about $\theta_1=35°$ for the neutral form. For the anionic form, the planar structure ($\theta_1=0°$) was the most stable conformation and the rotational barrier at $\theta_1=90°$ was ca. 59 kJ mol^{-1}. Considering that negative charge of the phenolate anion is delocalized into the vinyl moiety, as discussed above, the "planar structure" should be the most stable conformation, as indicated by our MO studies. The NMR studies showed that the coalescence temperatures of the two aromatic protons of the anionic and neutral forms of compound **9** were 62°C and below −70°C, respectively. These results indicate that the rotational barrier at $\theta_1=90°$ in the anionic form is much greater than that in the neutral form, supporting our MO results. Yoshikawa and Terada also reported a great reduction of the rotational freedom of compound **9** by a change from the neutral to the anionic form, based on NMR studies.[9] Although the reason for the difference between the conformational studies in the present study and those by Yoshikawa et al.[8] is not yet fully understood, it is reasonable to consider that the "planar structure" might be the most stable conformation of the anionic form of 4-(disubstituted vinyl)phenols represented by the general structure shown in Fig. 1.

We thank Mr. Yuji Nakamura, Central Research Institute, Ishihara Sangyo Kaisha Ltd., for facilitating use of an ^{1}H NMR spectrometer. We are grateful to Dr. Takashi Iwashita, Suntory Institute for Bioorganic Research, and Dr Naoki Higuchi, Bioorganic Chemistry Laboratory for Fundamental Research, Suntory Ltd., for the measurement of ^{13}C NMR spectra. We also thank Dr. Takamitsu Kobayashi, Chugai Pharmaceutical Co., Ltd., for his kind advice about MO calculations.

References

1) H. Miyoshi, T. Nishioka, and T. Fujita, *Biochim. Biophys. Acta*, **891**, 293 (1987).

2) H. Miyoshi and T. Fujita, *Biochim. Biophys. Acta*, **935**, 312 (1988).

3) H. Miyoshi, H. Tsujishita, N. Tokutake, and T. Fujita, *Biochim. Biophys. Acta*, **1016**, 99 (1990).

4) L. A. Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **85**, 3397 (1963).

5) C. H. Rochester and B. Rossall, *J. Chem. Soc. B*, **1967**, 743.

6) H. P. Hopkins and S. Z. Ali, *J. Am. Chem. Soc.*, **99**, 2026 (1977).

7) H. P. Hopkins and D. V. Jahagirdar, *J. Am. Chem. Soc.*, **106**, 4341 (1984).

8) K. Yoshikawa, N. Kumazawa, H. Terada, and M. Ju-ichi, *Bull. Chem. Soc. Jpn.*, **54**, 1108 (1981).

9) K. Yoshikawa and H. Terada, *J. Am. Chem. Soc.*, **104**, 7644 (1982).

10) M. Charton, *Prog. Phys. Org. Chem.*, **13**, 119 (1981).

11) I. Katsumi, H. Kondo, Y. Fuse, K. Yamashita, T. Hidaka, K. Takeo, T. Yamashita, and K. Watanabe, *Chem. Pharm. Bull.*, **34**, 1619 (1986).

12) A. S. Jones, G. Verhelst, and R. T. Walker, *Tetrahedron Lett.*, **1979**, 4415.

13) M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).

14) A. T Nielsen and W. J. Houlihan, "Organic Reactions," Wiley, New York (1968), Vol. 16, pp. 12.

15) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy, " Academic Press, New York (1969), pp. 358.

16) C. A. Kingsbury, D. Draney, A. Sopchik, W. Rissler, and D. Durham, *J. Org. Chem.*, **41**, 3863 (1976).

17) O. Exner, "Correlation Analysis in Chemistry," ed by N. Chapman and B. Shorter, Plenum Press, London (1978), pp. 456.

18) H. Gunther, "NMR Spectroscopy," Wiley, New York (1980), Chap. 6.

19) D. J. Gale, D. J. Craik, and R. T. C. Brownlee, *Magn. Reson. Chem.*, **26**, 275 (1988).