

RING-CHAIN TAUTOMERISM OF HALOGENATED PHENOLPHTHALEINS : VIBRATIONAL SPECTROSCOPIC AND SEMIEMPIRICAL MO STUDY

Ko-Ki Kunimoto,^{*a} Hiromasa Sugiura,^a Toshiyuki Kato,^a Hitoshi Senda,^a Akio Kuwae,^b and Kazuhiko Hanai^c

^aDepartment of Chemistry and Chemical Engineering, Faculty of Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan ^bInstitute of Natural Sciences, Nagoya City University, Nagoya 467-8501, Japan ^cGifu Pharmaceutical University, Gifu 502-8585, Japan
(E-mail : lee@kenroku.kanazawa-u.ac.jp)

Abstract – Ring-chain tautomerism of halogenated phenolphthaleins and the effect of the halogen substitution have been studied by vibrational spectroscopic and semiempirical MO methods. The vibrational spectra indicate that the content of the colored species (carboxylate form) increases on the substitution of the isobenzofuranone ring, whereas the colorless species (lactone form) becomes dominant on the substitution of phenolic rings. MO calculations have revealed that the substitution of either ring does not change the basic property of the electronic transition of the colored species and that the relative stability of both forms is dependent on the substitution type in accord with the results of the vibrational study.

INTRODUCTION

Phenolphthalein (PP) is a typical phthalein dye, having been used as a pH titration indicator and a laxative agent. Since the discovery by Baeyer,¹ extensive studies have been devoted to elucidation of the coloration mechanism of this dyestuff. These approaches include UV-VIS,^{2,3} IR, resonance Raman,^{4,5} and ¹H and ¹³C NMR^{6,7} spectroscopies. The spectroscopic results co-operatively suggested that the color change of PP occurs as a result of the proton dissociation in alkaline solution as shown in Figure 1. In this scheme, PP exists as the colorless lactone form (H₂PP) at pH 8 and lower. As the pH rises 8 to 10, both phenolic protons dissociate with approximately equal ease to form the dianion (PP²⁻). The carboxylate PP²⁻/C species is considered to be responsible for the red-pink color in alkaline solution. Various PP

derivatives have been developed in search for the dyes having color change intervals different from that of PP. Among these PP derivatives, alkyl-group substituted PPs such as thymolphthalein and cresolphthalein

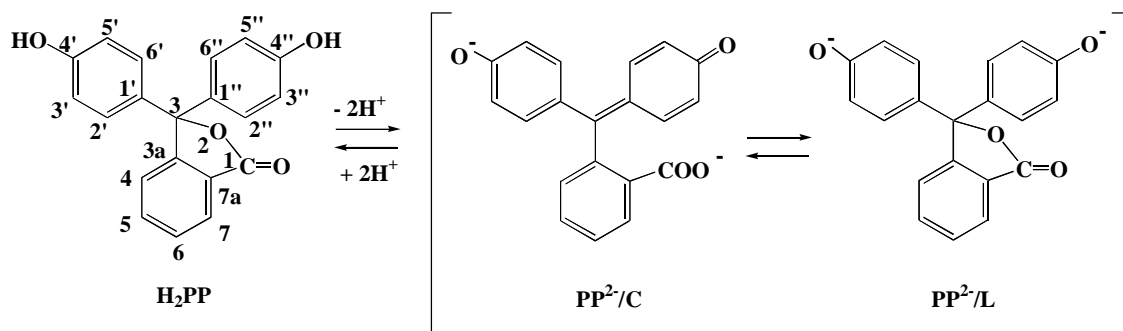


Figure 1 The structure change of PPs on the change of pH

are of much practical use as an acid-base indicator. On the contrary, halogenated PPs substituted on the phenolic rings are of little use for this purpose; the alkaline colors of halogenated PPs are too faint and unstable to be visually observed.⁸ These substituent effects on PP contrast with the case of sulfophthalein dyes where both the alkyl- and the halogen-substituted derivatives provide versatile acid-base indicators.⁹ The origin of the unusual coloration of halogenated PPs has not been studied until recently. Based on careful measurements of absorption spectra, Tamura and his co-workers suggested the involvement of the lactone PP^{2-}/L form in the alkaline solution of PP.¹⁰ This PP^{2-}/L species is considered to be colorless because three phenyl chromophores in the molecule are isolated at the C_3 carbon atom. Recently we have demonstrated through IR and Raman spectroscopy that the alkaline form of PP is a mixture of the colorless lactone PP^{2-}/L form and the colored carboxylate PP^{2-}/C form both in the solid state and in solution.¹¹ The equilibrium position between the colored and colorless species may be affected by the chemical nature of the ring substituents. In this work, we have prepared a series of PP derivatives where halogens are substituted at either the phenolic or the isobenzofuranone ring. IR and Raman spectra were examined for the dianionic forms of these dyes. Semiempirical MO calculations were carried out in order to interpret the effect of the halogen substitution on the electronic spectra and to estimate the relative stability of the molecular species.

EXPERIMENTAL

Materials

Halogenated PPs used in this work are listed in Table 1. 33-Cl, 33-Br, and 4567-Cl-PP were prepared through the conventional reaction of corresponding phthalic anhydrides and phenols with zinc chloride and/or sulfuric acid as catalysts.¹² Sodium hydroxide solutions of crude products were neutralized with hydrochloric acid and the precipitates were separated by filtration. This procedure was repeated several times. Furthermore, the crude products were purified through silica gel chromatography using hexane:chloroform (6:4) as an eluent. Purities of the compounds were checked by elemental analyses

Table 1 Chemical structures of phenolphthalein dyes

Common Name	Abbr.
Phenolphthalein	PP
3',3''-Dichlorophenolphthalein	33-Cl-PP
3',3''-Dibromophenolphthalein	33-Br-PP
3',3'',5',5''-Tetrachlorophenolphthalein	3355-Cl-PP
3',3'',5',5''-Tetrabromophenolphthalein	3355-Br-PP
Phenol-4,5,6,7-tetrachlorophthalein	4567-Cl-PP
Phenol-4,5,6,7-tetrabromophthalein	4567-Br-PP

and ^1H NMR measurements. Preparation of 3355-Cl-PP was unsuccessful and only the MO calculations were carried out for this compound. PP, 3355-Br-, and 4567-Br-PP were purchased from Tokyo Kasei Kogyo Co., Ltd. Disodium salts of PPs (PPs- Na_2) was prepared by mixing 1 mmol of each PP derivative in methanol with 2 mmol of sodium hydroxide solution. Subsequent evaporation of the solvent resulted in colored products.

Spectral Measurements

UV-VIS absorption spectra were recorded on a Hitachi U-2001 spectrophotometer by using a cell of 1 cm pathlength. Aqueous solutions of dyes (2×10^{-5} M) used contain 1 % methanol. The IR spectra were recorded on a Perkin Elmer 1650 FT-IR spectrophotometer by averaging 64 scans with a resolution of 4 cm^{-1} . The spectra of solid samples were measured as KBr pellets. FT-Raman spectra were obtained on a Perkin Elmer 2000R spectrophotometer by using the 1064 nm line of a Spectron SL300 Nd:YAG laser as an exciting source. The samples were sealed in glass capillary tubes.

MO Calculations

Semiempirical MO calculations were carried out with the MOPAC AM1 semiempirical method implemented in CAChe programs¹³ run on an IBM RISC 6000 computer. Electronic spectra were calculated by using the ZINDO program. Configuration interaction (CI) calculations included single excited configurations from the ground state, consisting of 22(occupied) x 22(virtual) configurations. The lactone (PP²⁻/L) and carboxylate (PP²⁻/C) forms were considered as a possible tautomer of the PP²⁻ species. The initial molecular geometry for the two forms was taken from the X-Ray structure of PP¹⁴ and the structure was optimized by the AM1 method. For the PP²⁻/L and PP²⁻/C forms, the lowest energy conformations were searched for with respect to the three dihedral angle angles, $\tau_1(\text{C}_2'-\text{C}_1'-\text{C}_3-\text{C}_{3a})$, $\tau_2(\text{C}_2''-\text{C}_1''-\text{C}_3-\text{C}_{3a})$ and $\tau_3(\text{O}_2-\text{C}_1-\text{C}_{7a}-\text{C}_{3a})$ by using the optimized search option of the CAChe MOPAC. In all cases, the PRECISE option was used to provide higher accuracy within this calculation. As to the halogen substituted PPs, hydrogen atoms of either the phenolic or the isobenzofuranone ring were substituted by respective halogen atoms and the structures were further optimized by the AM1 method. The AM1 optimized structures were used for calculation of the absorption spectra by the ZINDO method.

RESULTS AND DISCUSSION

UV-VIS absorption of halogenated PPs

Table 2 summarizes visible absorption data of halogenated PPs in aqueous alkaline solution. PP and halogenated PPs are colored pink to violet in alkaline solution and shows characteristic absorptions in the 550-600 nm region. In the absorption spectra, halogen substitution of either the phenolic or the isobenzofuranone ring results in a red shift of the λ_{\max} . The magnitude of this shift appears to depend on the number and the position of the substitution and the largest shift of 31.5 nm is observed for the 3355-Br-PP²⁻ case. In contrast to the effect on the λ_{\max} position, the absorption strength was affected differently by the number and the position of substitution. Halogenated PP²⁻s substituted at the isobenzofuranone ring exhibit the intense color comparable to that of PP²⁻. However, the halogenated PPs substituted at the phenolic rings show much weaker color. For example, the apparent molar absorption coefficient ϵ_{app} drops drastically from 30,350 of PP²⁻ to 3,510 of 33-Br-PP²⁻ and further to 332 of 3355-Br-PP²⁻. As discussed later, small ϵ_{app} value of 3355-Br-PP²⁻ is due to a small content of the PP^{2-}/C form in the tautomeric mixture. Because of this weakness of the alkaline color, the color transformations of the halogenated PPs are so weak and unclear that they are not suitable for pH indicators.}

Table 2 Observed and calculated absorption spectra of PP dianions

compound	Obsd ^{a)}			Calcd	
	color	λ_{\max}/nm	$\epsilon_{\text{app}}/(\text{mol cm})^{-1}$	λ_{\max}/nm	oscillator strength, f
PP ²⁻	pink-violet	552.0	30,350	494.3	1.15
33-Cl- PP ²⁻	pink	562.0	4,750	491.2	1.20
33-Br- PP ²⁻	pink	565.5	3,510	493.4	1.13
3355-Cl- PP ²⁻	^{b)}	^{b)}	^{b)}	492.4	1.17
3355-Br- PP ²⁻	colorless	583.5	332	492.4	1.13
4567-Cl- PP ²⁻	deep violet	574.0	38,250	508.7	1.14
4567-Br- PP ²⁻	violet	575.0	25,450	511.1	1.13

a) aqueous solution (10^{-3} - 10^{-4} mol/L)

b) see experimental section

IR and Raman Spectra of halogenated PP²⁻

Figures 2 shows the IR and Raman spectra of PP-Na₂ and its halogenated derivatives. As pointed out in the previous work, the PP^{2-}/L and the PP^{2-}/C species coexist in the solid state of PP^{2-}-Na₂.¹¹ The PP^{2-}/L species is characterized by the lactone C=O stretching mode ($\nu_{\text{C=O}}$) in the 1700 cm⁻¹ region, whereas the PP^{2-}/C species is characterized by the asymmetric COO⁻ stretching band (ν_{aCOO^-}) in the 1550 cm⁻¹ region. Thus the relative intensity of the $I(\nu_{\text{aCOO}^-}) / I(\nu_{\text{C=O}})$ in the IR spectra can be used as a criterion for the content of the PP^{2-}/C and the PP^{2-}/L species. Since the IR band around 1550 cm⁻¹ has also a contribution from the $\nu_{\text{C=C}}$ modes of the PP^{2-}/C species and the molecular absorptivities of the ν_{aCOO^-} and the $\nu_{\text{C=O}}$}}}}}}}}

bands may be changed on ring halogenation, the relative intensity, $I(\nu_{\text{aCOO}^-}) / I(\nu_{\text{C=O}})$ should be considered as a rough measure. Inspection of the IR spectra shows that the relative intensities $I(\nu_{\text{aCOO}^-}) / I(\nu_{\text{C=O}})$ of 4567-Cl-PP-Na₂ and 4567-Br-PP-Na₂ are greater than that of PP-Na₂. Conversely, in the PP²⁻s halogenated at the phenolic rings such as 33-Cl-PP-Na₂ and 33-Br-PP-Na₂, it decreases and becomes very small for 3355-Br-PP-Na₂. This trend is also evident in the Raman spectra. In the Raman spectra, the quinone-phenolate ring modes of the PP²⁻/C species are observed intensely in the 1560-1620 cm⁻¹ region and the lactone C=O stretching of the PP²⁻/L species are observed very weakly. This is because Raman spectra are more sensitive to the colored PP²⁻/C species owing to partial resonance Raman effect. The vibrational observations show that the content of the colored PP²⁻/C species increases on the halogen substitution of the isobenzofuranone ring and the colorless PP²⁻/L species becomes dominant on the halogen substitution of the phenolic rings.

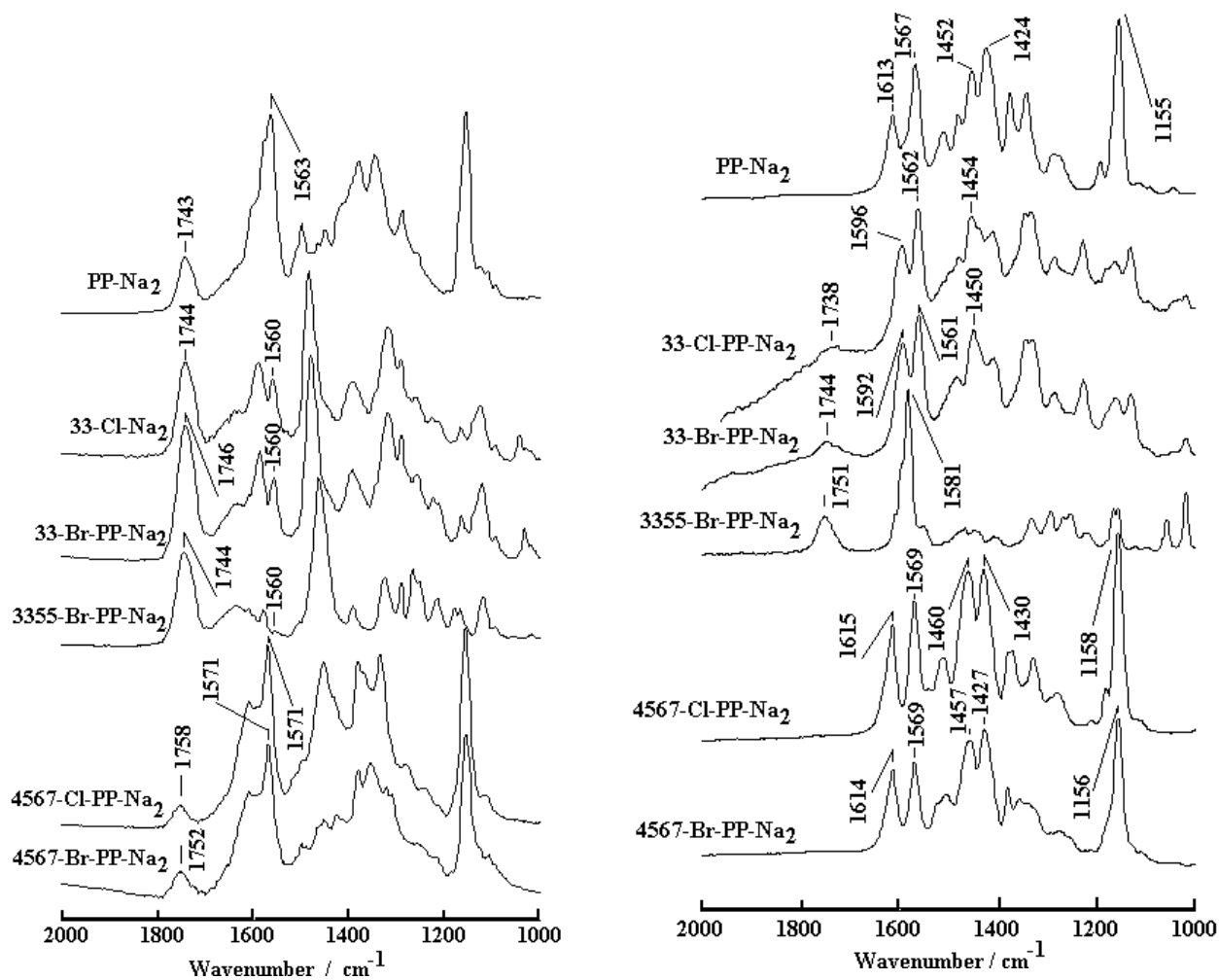


Figure 2 IR (left) and Raman (right) spectra of PP-Na₂ and its halogenated derivatives in the solid state

MO calculations

In order to interpret the substitution effect on the visible absorption, the absorption spectra were calculated for both the PP²⁻/L and the PP²⁻/C species by the ZINDO method. The calculation result for the PP²⁻/L

form does not give rise to any significant absorption in the visible region. This is because the three π systems are insulated by the C₃ carbon atom with the sp³ nature. The PP²⁻/C form, on the other hand, gives the absorption maxima in the 490-510 region as shown in Table 2. The calculated λ_{max} values for the PP²⁻ species are generally shifted about 60 nm to a shorter wavelength compared to the observed; this tendency is frequently seen for the calculation using the INDO parametrization.¹⁵ These absorption bands correspond to HOMO-to-LUMO transitions, which take place between the delocalized orbitals of the quinone-phenolate system in the PP²⁻/C form. Similar transition profiles are obtained for the halogenated derivatives. Thus, the coloration of PP-Na₂ and its halogenated derivatives are ascribed to the π - π^* electronic transition of the resonating structure of the PP²⁻/C species. The calculated oscillator strengths are practically unaffected by the halogen substitution and in the range of 1.15-1.25. These results indicate that the halogen substitution on either the phenolic or the isobenzofuranone ring does not change the basic property of the electronic transition of the PP²⁻/C species.

As a next step, we calculated the optimized conformations for PP and its derivatives in the PP²⁻/L and the PP²⁻/C form. As shown in Table 3, the optimized conformation of the PP²⁻/L form is similar for all the halogenated derivatives and close to that of the X-Ray structure of PP.¹⁴ Thus the two phenolic rings

Table 3 AM1 results for PP²⁻ and its halogenated derivatives

Compound	Dihedral angles of optimized structures / °						ΔH_f / kcal mol ⁻¹		
	L form			C form			L form	C form	$\Delta\Delta H_f$ ^{a)}
	τ_1	τ_2	τ_3	τ_1	τ_2	τ_3			
PP ²⁻	85.9	-12.1	0.4	32.7	10.1	75.2	-71.8	-76.1	+4.3
33-Cl- PP ²⁻	86.1	-13.6	0.8	31.6	11.7	69.9	-96.8	-94.8	-2.0
33-Br- PP ²⁻	85.4	-14.1	0.5	29.3	14.9	63.5	-76.1	-72.8	-3.3
3355-Cl- PP ²⁻	86.1	-11.6	0.8	32.8	10.9	71.5	-117.8	-112.4	-5.4
3355-Br- PP ²⁻	86.6	-12.0	0.9	32.3	10.7	71.7	-75.1	-67.6	-7.5
4567-Cl- PP ²⁻	74.1	-15.2	0.7	31.9	10.4	86.6	-94.7	-102.1	+7.4
4567-Br- PP ²⁻	68.0	-12.7	1.4	31.4	11.3	88.6	-49.3	-57.5	+8.2

a) $\Delta\Delta H_f = \Delta H_f$ (L form) – ΔH_f (C form)

twist about 70° to each other and the central C3 carbon has a typical sp³ nature. In the PP²⁻/C form the twisting angle reduces to about 40° and the two phenolate rings tend to align coplanar. This conformation endows the sp² character to the central C3 carbon atom and facilitates π electron delocalization over the quinone-phenolate ring system. Inspection of heats of formation indicates that for PP²⁻ itself the carboxylate form is thermodynamically more stable than the lactone form. Halogen substitution of the isobenzofuranone ring appears to reinforce the relative stability of the PP²⁻/C form over the PP²⁻/L form. On the other hand, the substitution of the phenolic rings appears to make the PP²⁻/L form more stable than the PP²⁻/C form. The conformational preferences of PP²⁻ and its halogenated derivatives qualitatively

agree with the visible absorption and IR data.

CONCLUSION

The halogen substitution of either ring does not change the electronic transition property of the colored species. The relative stability of both forms depends on the substitution type; the substitution of the isobenzofuranone ring stabilizes the PP²⁻/C form, but that of the phenolic ring makes the PP²⁻/L form more stable than the PP²⁻/C form. Thus, it is the tautomeric [PP²⁻/C]/[PP²⁻/L] ratio that determines the alkaline color of the halogenated PPs.

ACKNOWLEDGEMENTS

The authors are grateful to Mrs. M. Hosokawa and Mrs. M. Hayashi of Gifu Pharmaceutical University for the elemental and MS spectral analyses.

REFERENCES

1. A. v. Baeyer, *Ber.*, 1871, **4**, 658.
2. T. Ozeki, H. Morikawa, and H. Kihara, *Bunseki Kagaku*, 1994, **43**, 339.
3. Z. Tamura, S. Abe, K. Ito, and M. Maeda, *Anal. Sci.*, 1996, **12**, 929.
4. M. Davies and R. L. Jones, *J. Chem. Soc.*, 1954, 120.
5. S. Chattopadhyay, G. S. Kastha, S. K. Nandy, and S. K. Brahma, *J. Raman Spectrosc.*, 1989, **20**, 651.
6. E. Ziegler and H. Sterk, *Monatsh.*, 1969, **100**, 1604.
7. S. Berger, *Tetrahedron*, 1981, **37**, 1607.
8. I. M. Kolthoff and C. Rosenbaum, *Acid-Base Indicators*, MacMillan, New York, 1937.
9. *The Sigma-Aldrich Handbook of Stains, Dyes and Indicators*, ed. by F. J. Green, 1990, Aldrich Chemical Co. Inc., Milwaukee, Wisconsin.
10. Z. Tamura and M. Maeda, *Yakugaku Zasshi*, 1997, **117**, 764.
11. K. Kunimoto, H. Sugiura, T. Kato, H. Senda, A. Kuwae, and K. Hanai, *Spectrochim. Acta, Part A*, 2001, **57**, 265.
12. M. Yamamoto, M. Kumaki, and S. Ohara, *Eisei Shikensho Hokoku*, 1940, **55**, 83.
13. CAChe Work System ver. 3.8, CAChe Scientific, Inc, Oxford Molecular Group, Beaverton, OR, 1995.
14. H. Sugiura, T. Kato, H. Senda, K. Kunimoto, A. Kuwae and, K. Hanai, *Anal. Sci.*, 1999, **15**, 611.
15. M. Adachi and S. Nakamura, *Dyes and Pigments*, 1991, **17**, 287.