Available online at www.sciencedirect.com
SCIENCE DIRECT®
Dyes and Pigments 59 (2003) 251–261
DYES and PIGMENTS
www.elsevier.com/locate/dyepig

Structure and properties of some cresolphthalein derivatives

William E. Brenzovich Jr., Misty D. Odell, Joana P. Soares, Christopher J. Abelt*

Department of Chemistry, College of William and Mary, Williamsburg, VA 23187-8795, USA

Received 16 January 2003; received in revised form 24 February 2003; accepted 4 June 2003

Abstract

The following cresolphthalein (CP) derivatives are prepared from 5,5′-dibromocresolphthalein (**3**): 5,5′-dicyano (**7**), 5,5′-dicarbomethoxy (**9**); 5-bromo-5′-cyano (**8**), 5-bromo-5′-carbomethoxy (**10**), monomethyl ether (**11**) and 5,5′-dibromo monomethyl ether (**13**). The lactone ring remains intact in the monobasic forms of **11** and **12**. The dibasic forms of the CP derivatives **3** and **8**–**10** show long-wavelength absorption bands, but exist mainly as the closed lactone structure. The dibasic form of **7** does not show long-wavelength absorption and exists only as the closed lactone structure. The proportion of ring-closed dianion goes as the electron-withdrawing ability of the substituents, and it increases in the order $H < Br < CO_2CH_3 < CN$. Acidity constants are reported. They correlate with acidity of the related phenols, but not with the electronic characteristics of the substitutents. The first and second ionization constants are well-resolved in the unsymmetrical derivatives **8** and **10**. AM1 calculations predicting optimal structures, uv/vis transitions and various equilibria are reported.
© 2003 Elsevier Ltd. All rights reserved.

Keywords: Phthalein indicators; Lactone ring-opening isomerization

1. Introduction

Phenolphthaleins and their derivatives are well known as pH indicators [1,2]. In neutral solution phenolphthalein exits primarily as the colorless γ-lactone (**1a**, Fig. 1), whereas the dibasic form has a highly colored ring-opened structure (**1g**). In neutral to basic solution, phenolphthalein may assume no fewer than nine possible structures (**1a–i**) [3–5]. Although the transition from the neutral to the dibasic form must involve at least two ionization constants, these indicators are usually characterized by a composite constant assigned as the pH where the absorption of the colored dibase is 50% of maximum. A curve-fitting method has been used to determine the first and second ionization constants of phenolphthalein. They are very close in magnitude: pK_1 is 9.05 and pK_2 is 9.50 [6].

Our interest in the phthaleins is in their possible use as a pH sensitive switch for supramolecular systems. In the transition from the colorless to colored form, the carbon attached to all three aryl groups rehybridizes from sp^3 to sp^2, and the molecule becomes doubly negatively charged. If the phthalein were attached to a host molecule such as β-cyclodextrin, then a structural change in the phthalein portion might affect the structure and properties of the host portion.

* Corresponding author. Tel.: +1-757-221-2551; fax: +1-7575-221-2715.
E-mail address: cjabel@wm.edu (C.J. Abelt).

0143-7208/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0143-7208(03)00116-5

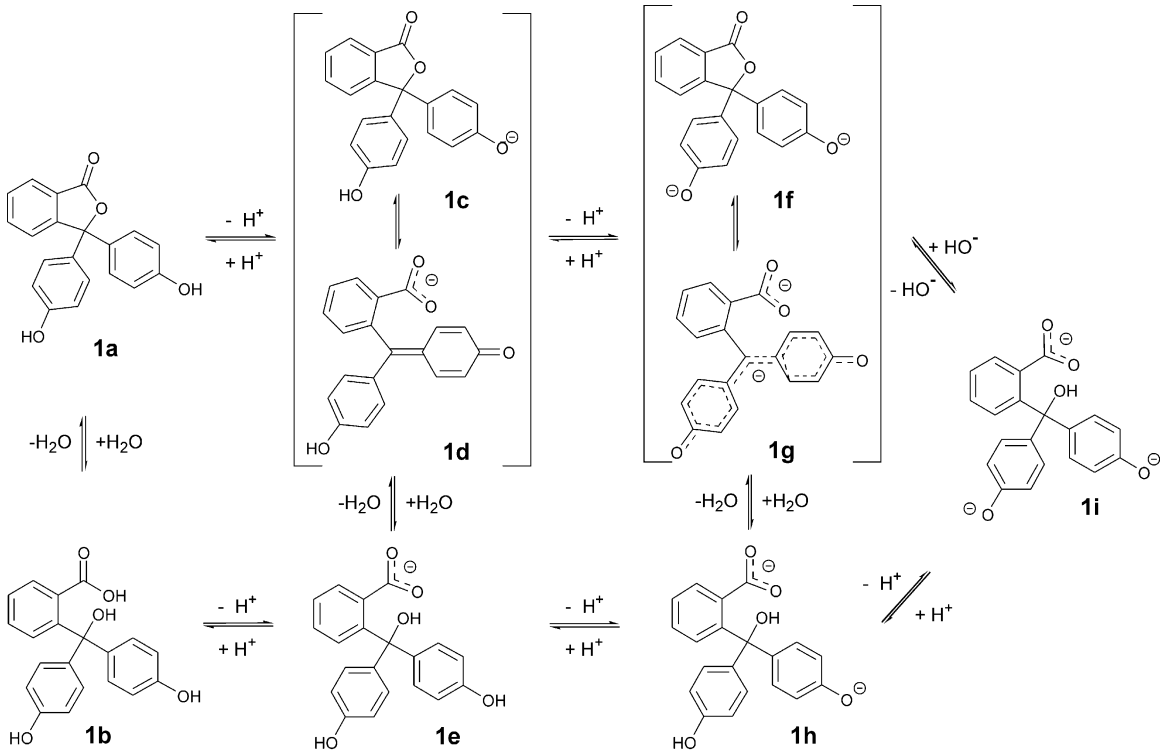


Fig. 1. Neutral and basic forms of phenolphthalein.

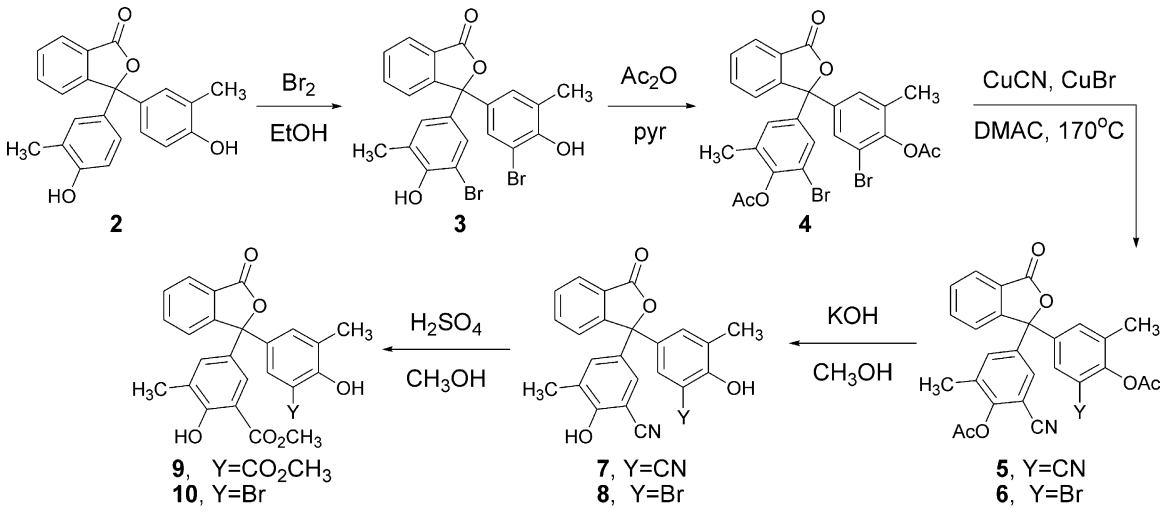
We sought to synthesize a phenolphthalein with carboxylate groups adjacent to the phenolic hydroxyl groups in order to cap cyclodextrin to the phthalein via ester or amide bonds. In this paper we report the synthesis of cresolphthalein derivatives **3**, **7**–**11**, **13**, and the structures of their basic forms.

2. Results and discussion

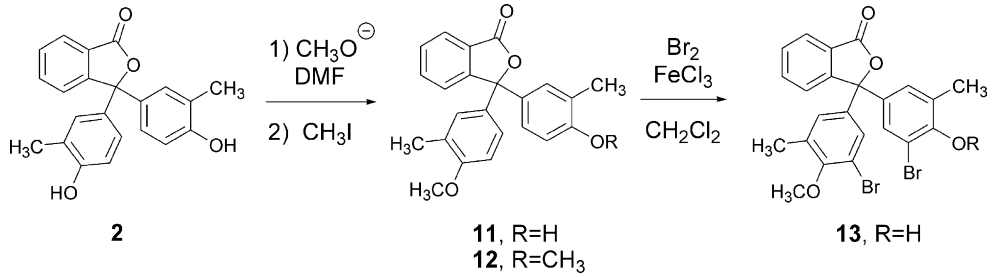
2.1. Synthesis

The preparation of cresolphthalein derivatives **3**–**10** is shown in Scheme 1. We chose cresolphthalein (**2**) over phenolphthalein (**1**) because the two extra methyl groups in the former block two of the four activated *ortho* positions. Bromination of cresolphthalein proceeds quantitatively at the two available *ortho* positions. The cyanation step requires protection of the phenolic hydroxyl groups as acetate esters. Cyanation with CuCN is not straightforward in that it rarely gives complete conversion. Palladium catalyzed cyanation with $Pd_2(dba)_3$ and $Zn(CN)_2$ [7] is not efficacious in this case, and give only two-thirds conversion. We find that addition of CuBr provides the best conversion, in accord with the literature [8]. The major side product, 5-cyano-5′-bromocresolphthalein diacetate (**6**), comprises up to 10% of the product mixture. After the acetate protecting groups are removed, 5-bromo-5′-cyanocresolphthalein (**8**) and 5,5′-dicyanocresolphthalein (**7**) can be separated by simple column chromatography. Acidic methanolysis converts the nitrile groups to carboxymethyl groups.

Because it is difficult to distinguish the first and second ionization of phthaleins, we wanted to make CP derivatives where the second ionization is blocked. Methylation of **2** predictably gives a mixture of methyl and dimethyl ethers, **11** and **12**, resp., along with unreacted **2** (Scheme 2). Compounds **2** and **11** are both acidic, and they are separated from **12** by extraction with hot dilute



Scheme 1. Synthesis of cresolphthalein derivatives.



Scheme 2. Synthesis of cresolphthalein methyl ethers.

base. Washing the ether solution of **2** and **11** repeatedly with cold dilute base removes **2** completely. In contrast to the facile reaction with **2**, bromination of **11** requires a Lewis acid catalyst for complete conversion.

2.2. Spectroscopic properties

Spectroscopic data for dibasic forms of several CPs are shown in Table 1. Included in the table are data for the related phenoxides and CP ethers and calculated electronic transitions (vide infra). All CPs except **7** show the long-wavelength absorption band characteristic of the phthaleins. This band is very intense only with **2**, but it is an order of magnitude smaller with the rest. Both **2** and **3** have a shorter wavelength band (ca. 380 nm) that is associated with long-wavelength band. All of the dibasic CPs have a short-wavelength band around 300 nm that is similar to the band of the corresponding phenoxide. The unsymmetrical CPs **8** and **10** show the absorptions of both phenoxides. The CP methyl ethers **11** and **13** show only phenoxide-like absorptions.

The long-wavelength absorption band arises from the ring-opened form of the dianion (c.f. **1g**, Fig. 1). The ring-opened form has an extended phenolate-quinomethane π-system that gives rise to a low electronic transition energy. Both the ring-opened and closed dianions (c.f. **1f**, Fig. 1) will show an absorption band that resembles the band of the related phenoxide. This facet is shown through complexation studies of phenolphthalein with β-cyclodextrin. [9,10] Inclusion of the open dianion form (**1g**) with cyclodextrin gives the dianion lactone (**1f**). Titration of **1g** with cyclodextrin

Table 1
Spectroscopic data and calculated absorptions for dibasic cresolphthaleins and model anions in 50% wt% EtOH-H_2O

Cresolphthaleins							Phenols			Cresolphthalein ethers		
	Experimental		Calculated					Experimental			Experimental	
			Open		Closed							
No.	λ_{max} (nm)	$\epsilon\times10^{-4}$	λ (nm)	$f\times10$	λ (nm)	$f\times10$	No.	λ_{max} (nm)	$\epsilon\times10^{-4}$	No.	λ_{max} (nm)	$\epsilon\times10^{-4}$
	572	4.8	541	6.5								
2	378	0.7	378	1.5	327	1.3	14	292	0.4	11	297[a]	0.5
	296	1.4	304	1.6	299	3.2						
	589	0.6	543	7.1								
3	383	0.1	376	1.7	339	1.8	15	299	0.6	13	299[a]	0.5
	299	1.0	300	1.4	306	2.3						
	554	7.2										
7	335	1.1	328	2.1	335	2.9	16	330	0.6			
	300	1.7										
	573	0.3	543	7.7								
9	340	0.9	331	1.9	332	2.4	17	337	0.6			
	299	1.0	293	1.1								
	536	0.1	498	6.9								
8	334	0.6	356	1.9	340	1.6						
	304	0.7	300	1.2	310	1.7						
	582	0.3	542	7.8								
10	339	0.4	351	2.3	338	1.6						
	299	0.6	300	1.5	308	1.5						

[a] Shoulder.

results in the extinction of the long-wavelength band, but only a small decrease in the short-wavelength band at 290 nm. [11] Cyclodextrin inclusion does not extinguish the long wavelength bands for cresolphthalein dianion because the extra methyl groups in **2** weaken the strength of the complex. [11,12] Calculations indicate that the long-wavelength band of the open form should be several times more intense than the localized transition of the phenoxide. The fact that the long-wavelength band is much weaker than the short-wavelength bands for **3** and **7**–**10** is evidence for a small proportion of ring-opened form of the dianion. Using the calculated oscillator strengths for the long and short-wavelength transitions, we estimate the percentage of open form as follows: **2**, 92%; **3**, 18%; **7**, 0%, **8**, 3%; **9**, 9%, **10**, 10%. Thus, the substituents favor the closed dianion structure in the order $H < Br < CO_2CH_3 \leqslant CN$.

The results with CP methyl ethers **11** and **13** show that the mono basic forms have intact lactone rings. The ring-opened structures would be expected to show absorptions near the visible region. Instead, only short-wavelength bands associated with the phenoxide groups are observed.

2.3. Acidity properties

The pK_a values for the CPs, CP ethers and phenols in 50 wt.% aq. EtOH are shown in Table 2. The CP ethers and phenols both have only one acidic proton, and their ionization constants are determined by the inflection point in the plot of

Table 2
Acidity constants[a] for cresolphthaleins and related compounds in 50 wt% EtOH-H_2O

Cresolphthaleins				Phenols		Cresolphthalein ethers	
No.	inflection	pK_{a1}	pK_{a2}	No.	pK_a	No.	pK_a
2	10.9			14	11.2	11	10.8
3	9.6	8.8[b]	9.4[b]	15	9.7	13	8.9
7	6.7	6.3[c]	7.2[c]	16	8.2		
9		10.9	11.7	17	11.0		
8		6.7	9.5				
10		9.0	11.7				

[a] The standard deviation of multiple runs is less than 0.1.
[b] Determined by interative deconvolution where the mono base and dibase can be distinguished.
[c] Determined by interative deconvolution assuming that the dibase is completely closed and that the absorbance of the dibase is twice that of the mono base.

absorption vs pH. The CPs have two acidic protons and thus two ionization constants. The ionization constants of the unsymmetric CPs (**8**, **10**) are very different and can be determined from the inflection points. The titration curves for the symmetric CPs (**3**, **7**, **9**) show only a single inflection point. Deconvolution of the plots using a curve-fitting procedure is necessary to elucidate the pK_a values. [6,13] We were not able to deconvolute the titration curve of cresolphthalein (**2**) itself.

The pK_a values for the CP derivatives closely follow those of the related phenols. The values for the first ionization are invariably smaller, whereas the values for the second ionization are smaller for all but the carbomethoxy derivatives **9** and **10**. None of the phenol models have methyl groups in the *ortho*-position or alkyl groups in the *para*-position. These groups would increase the pK_a values, and make the difference between the CP derivatives and phenol models greater. Since the first ionization of the CP derivatives gives a localized phenolate anion, it follows that the other two aryl groups must stabilize the anion to account for the enhance acidity. While the pK_a values of the CP derivatives follow those of the related phenols, they do not follow the electronic nature of the *ortho*-substituent. The outlying behavior occurs with the carbomethoxy group. This substituent forms a H-bond with the adjacent phenolic OH group. Ionization breaks this bond, raising the relative energy for ionization, and hence the pK_a, of these substrates [14].

2.4. Computational modeling

The thermodynamics and uv/vis spectra of the cresolphthaliens were studied using the AM1 semiempirical method. Geometrical optimization calculations were carried out on the neutral, monobasic and dibasic forms of **2**–**3** and **7**–**10**. Two structures were considered for the ionized forms: one with an intact lactone (ring-closed) and one where the lactone was broken (ring-opened). For each of these forms, minimum energy structures were calculated from distinct input conformations varying the dihedral angles shown in Fig. 2. For the carbomethoxy derivatives **9**–**10** two conformations of the ester group were considered. The minimum energy conformer for each species was used in the energy and spectral calculations. The free energies were calculated from thermodynamics (frequency) calculations. The effect of solvation was studied using the SM5.2 method [15].

The structure optimization results showed a number of common features for the various derivatives. Rotation about the C_{bz}–C1 bond gave small changes in the heat of formation, whereas the conformation of the phenolic hydroxyl had a larger effect. Pointing the hydroxyl at the substitutent (Br, CN, and CO_2CH_3) always resulted in the lowest energy structure. In the ring-opened

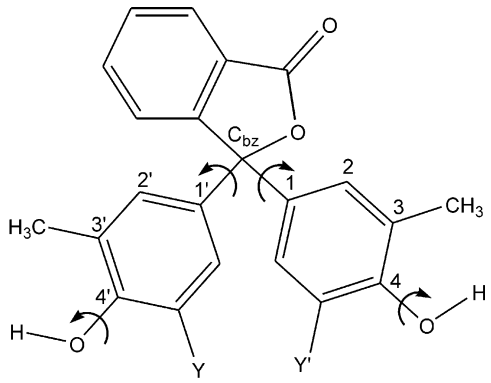


Fig. 2. Dihedral angles varied in structural optimisations.

structures of the monobasic and dibasic forms, one of the phenol rings is fully conjugated with the benzylic carbon, while the other is significantly twisted. The carboxylate group prefers to be perpendicular to the benzene ring and essentially parallel to the diphenylmethane moiety. Structures in which the carboxylate was forced to be planar with the attached benzene ring gave higher energies. The relative twist of the two phenol(ate) rings decreases going from the neutral to the anion and from the anion to the dianion. Small twist angles favor resonance delocalization of the negative charge.

The electronic transitions for the open and closed forms of the dibasic forms were calculated using the configurational interaction (C.I.) method in AMPAC. While PPP and CNDO methods are often useful for predicting absorption properties, [16] the implementation of C.I. in AMPAC allows for large and efficient calculations that have greatly improved the prediction of uv/vis spectra for this method. Here the number of C.I.-active molecular orbitals was set to the number of π-atoms. These calculations were performed on the geometry optimized structures above that had been reoptimized using Solvent Model 5.2 specifying water as the solvent. As shown in Table 1, the prediction of the transition frequencies is excellent for wavelengths less than 400 nm. The calculations underestimate all of the long wavelength absorptions by 30–46 nm. In contrast, calculations that do not include solvation overestimate the long wavelength band by a similar amount. Solvent clearly affects the position of this absorption, and it appears that the SM5.2 model overestimates the solvent interaction (vide infra). The predicted oscillator strength for the long wavelength absorption is about five times larger than the localized phenolate absorption. Thus, the ratio of these band intensities is an indicator of the position of the equilibrium between the open and closed dibasic forms.

The thermodynamics of the two ionization steps were examined. The values reported in Table 3 are the energy differences between the ionization of the various derivatives relative to the smallest energy of ionization; i.e., the smallest energy of reaction is set to zero. Ideally, the relative energies should correlate linearly with the experimental ionization constants. In fact, the correlations are reasonable if the data for ionization adjacent to a carbomethoxy group is discarded. The correlations of the first ionization with all but the gas phase ΔG values are reasonable ($R^2 > 0.96$, Fig. 3). The best correlation is with the gas phase ΔH. With the second ionization the correlations are worse, and none of the R^2 values are greater than 0.95 despite ignoring the data points for **9** and **10**. Here again, the best correlation is with the gas phase ΔH. The computational results corroborate the effect of electron withdrawing groups in lowering the pK_a values. The pK_a values of the carbomethoxy derivatives are higher than predicted because of the H-bonding between the carbomethoxy group and the phenolic hydroxyl group. Evidently, the calculations do not accurately model this stabilizing interaction.

Table 3
Calculated relative energies[a] of ionizations for cresolphthaleins

	1st ionization				2nd ionization			
	ΔH	ΔG	ΔH/SM5.2	ΔG/SM5.2	ΔH	ΔG	ΔH/SM5.2	ΔG/SM5.2
2	14.7	14.8	11.8	11.8	13.9	11.4	7.6	6.3
3	7.1	3.9	6.8	7.6	8.1	11.9	3.1	2.2
7	0.0	0.0	1.5	1.1	0.0	0.0	0.0	0.0
9	7.2	5.3	5.2	2.6	6.5	4.2	5.2	4.0
8	1.6	0.9	0.0	0.0	5.8	6.7	5.3	4.3
10	6.6	4.8	6.9	7.3	7.7	7.5	2.9	1.3

[a] AM1, kcal/mol.

The energies for the ring-open isomerization of the mono and dibases are shown in Table 4. Unlike the ionization case, the isomerization energies correspond to real values since the reaction energy is simply the difference in the heats of formation. The experimental results suggest that the mono bases exist largely in the closed form. The computational results confirm this observation with all derivatives except cresolphthalein itself. Here, only the ΔH calculation shows that ring-opening is endothermic. The results for the structures of the dibases are more relevant. The thermodynamics of this process determine the intensity of the characteristic phthalein color. The calculations for the gas phase indicate that the ring-

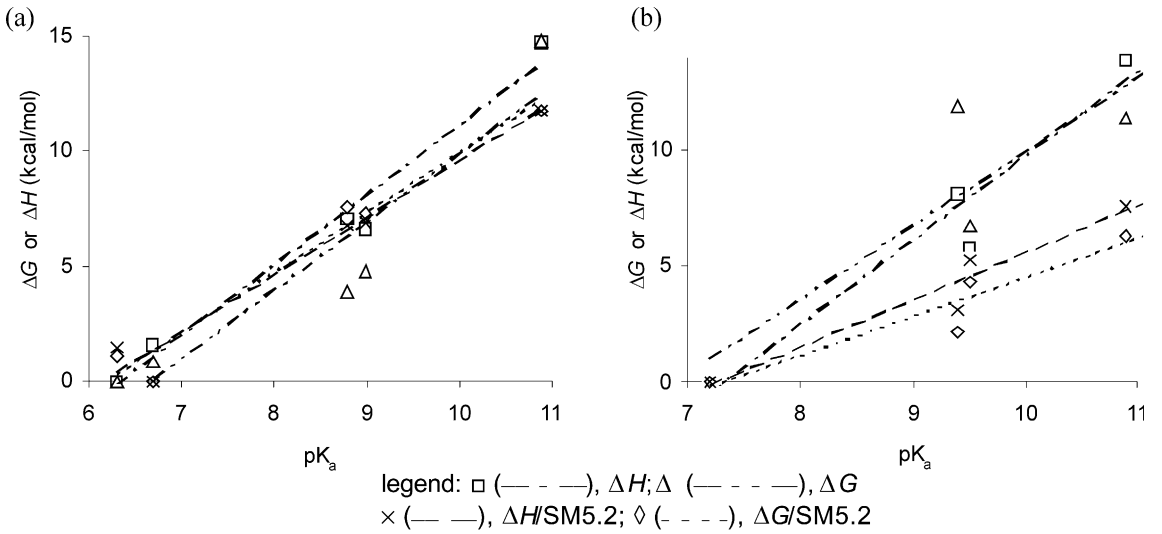


Fig. 3. Plots of computed, relative 1st (A) and 2nd (B) ionization energies vs. experimental pK_a.

Table 4
Calculated energies[a] for ring-opening of cresolphthalein bases

	Mono base				Dibase			
	ΔH	ΔG	ΔH/SM5.2	ΔG/SM5.2	ΔH	ΔG	ΔH/SM5.2	ΔG/SM5.2
2	2.4	−0.5	−2.3	−3.8	−3.2	−1.7	−5.8	−6.0
3	7.9	9.0	3.7	0.9	2.6	−0.4	−3.0	−2.6
7	11.6	10.3	5.1	6.9	6.7	3.7	2.2	7.5
9	11.4	10.5	6.4	7.9	7.9	7.9	1.4	1.4
8	12.8	13.4	8.2	8.9	4.6	1.7	−2.0	−2.6
10	8.3	8.1	3.5	2.1	4.6	2.6	−1.6	−1.6

[a] AM1, kcal/mol.

closed forms are favored, while those incorporating the solvation model show preference for the ring-opened structures. All agree that the dibasic form of 7 is ring-closed. Fig. 4 shows that correlation of these energies with the log of the estimated equilibrium constants (vide supra) is poor ($R^2 < 0.59$) for the gas phase values and marginal for the solvent model values ($R^2 > 0.67$). Again it appears that the solvation model more accurately reflects the trends, but it overestimates the magnitude of the solvation of the ring-opened, delocalized dibasic structures.

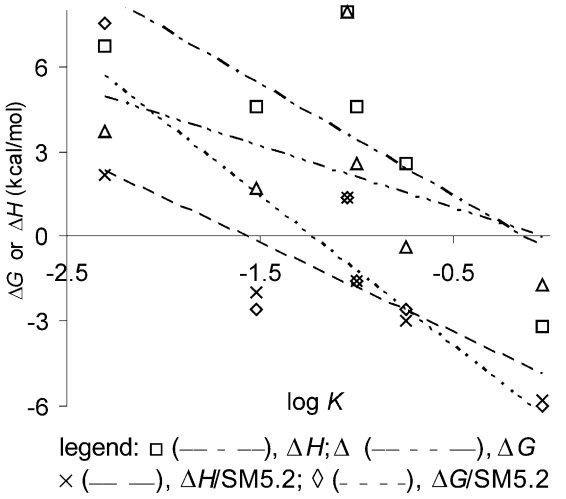


Fig. 4. Plot of computed energies for ring-opening of the dibases vs. log K.

3. Conclusions

Incorporating electron-withdrawing *ortho*-substituents into cresolphthalein greatly increases the acidity of the phenolic moieties. They also affect the absorption properties of the dibasic forms. The characteristic long-wavelength absorption

band of the dibasic form of the CP derivatives is weakened relative to cresolphthalein, and it is completely absent in the dicyano analog. These results are interpreted in terms of an energetic preference for the ring-closed lactone form of the dianion over the ring-opened form. The monomethyl ether derivatives show that the monoanions exist solely as the ring-closed form. Calculations support these generalizations, and reproduce the short-wavelength electronic transitions. The long-wavelength absorptions are not reproduced as well as the short-wavelength absorptions even with the solvation correction term.

The preponderance of the ring-closed form is problematic for the switching properties of these derivatives. Even the dibromo derivative **3** is a poor switch despite the presence of the two electron-donating methyl groups. Any substitution, therefore, must be made with electron-donating groups to favor the ring-opened structure in basic solution.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained using a Varian Mercury VX-400 spectrometer. Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. TLC was carried out using 0.25-mm HLF precoated silica gel plates (Analtech). Combustion analysis was performed by Desert Analytics.

Cresolphthalein and the model phenols were obtained from Aldrich or Acros. Copper (I) cyanide was prepared by the bisulfite reduction of copper (II) nitrate in the presence of sodium cyanide [17].

4.2. Synthesis

4.2.1. 4.2.1 5,5′-Dibromocresolphthalein [18]

Cresolphthalein (28.0 g, 80.8 mmol) is dissolved in EtOH (400 ml). The solution is cooled to 5 °C in an ice-bath. Bromine (28.0 g, 175 mmol) is weighed into benzene (25 ml), and the bromine solution is poured slowly into the cresolphthalein solution in one portion. The ice-bath is removed after several min, and stirring is continued overnight. The yellow solid that forms is collected by suction filtration, washed with cold EtOH, and air-dried giving 31.9 g (63.3 mmol, 78%): mp 257–260 °C; $R_f = 0.64$ (1:1 C_6H_{14}/EtOAc); ^{1}HNMR ($CDCl_3$): 2.24 (*s*, 6H), 5.64 (*s*, 2H), 7.00 (*d*, $J = 2.2$ Hz, 2H), 7.22 (*d*, $J = 2.2$ Hz, 2H), 7.52 (*d*, $J = 7.7$ Hz, 1H), 7.58 (*dd*, $J = 7.4$, 7.9 Hz, 1H), 7.73 (*dd*, $J = 7.4$, 7.7 Hz, 1H), 7.94 (*d*, $J = 7.9$ Hz, 1H); ^{13}CNMR ($CDCl_3$). Anal. Calcd. for $C_{22}H_{16}Br_2O_4$: C, 52.41; H, 3.20. Found: C, 52.54; H, 3.16.

4.2.2. 5,5′-Dicyanocresolphthalein

5,5′-Dibromocresolphthalein (31.9 g, 63.3 mmol) is stirred with Ac_2O (140 ml) and pyridine (15 ml) overnight. The mixture is poured into ice water (750 ml), the mixture is stirred as long as possible, then left to stand overnight. The solid is collected by suction filtration, washed with water, and dried to a constant mass leaving 37.0 g (62.8 mmol, 99%) of the diacetate: mp 162–164 °C; $R_f = 0.57$ (1:1 C_6H_{14}/EtOAc); ^{1}HNMR ($CDCl_3$): 2.16 (*s*, 6H), 2.36 (*s*, 6H), 7.16 (*d*, $J = 1.9$ Hz, 2H), 7.39 (*d*, $J = 1.9$ Hz, 2H), 7.58 (*d*, $J = 7.8$ Hz, 1H), 7.61 (*dd*, $J = 7.5$, 7.7 Hz, 1H), 7.76 (*d*, $J = 7.5$, 7.8 Hz, 1H), 7.96 (*d*, $J = 7.7$ Hz, 1H); ^{13}CNMR ($CDCl_3$) 17.3, 20.7, 89.6, 117.1, 124.1, 125.3, 126.6, 128.9, 129.2, 130.1, 133.4, 134.9, 139.3, 147.5, 150.6, 168.0, 169.0.

5,5′-Dibromocresolphthalein diacetate (23.84 g, 40.5 mmol) is dissolved in DMAC (400 ml, freshly distilled under Ar, b.p. > 165 °C). CuCN (23.80 g, 266 mmol) and CuBr (11.92 g, 83.1 mmol) are added, and the mixture is immersed in a preheated oil bath (180 °C). Stirring is continued for 1 h, then most of the DMAC is removed by simple distillation under N_2. The residue is cooled and poured into rapidly stirring ice water. The resulting solid is collected by suction filtration, air-dried, and left to dry in the open overnight. The solid is digested with boiling aq. HNO_3 (400 ml, 1:3 dilution) over 5 min (caution! HCN can be released! Adequate ventilation is required!). The digestion is complete after the sudden release of brown gas, and boiling is continued for no more than 2 min after this point. Ice is added, and the solid is collected by suction filtration. The solid is ground, washed with water, suction-filtered, and

left to dry over several days. The resulting solid (21.67 g) is dissolved in 2.4% methanolic KOH (500 ml), and the mixture is heated at gentle reflux overnight. The mixture is cooled and filtered. The filtrate is treated with the following and filtered after each step: 5% aq. AcOH (20 ml), water (200 ml), 5% aq. HOAc (20 ml), and 5% aq AcOH (1300 ml). The solid caught with the final treatment is washed with water and dried leaving 14.57 g (38.5 mmol, 91%). The product contains up to 10% 5-bromo-5′-cyanocresolphthalein from incomplete conversion. Separation from the monobromo compound is accomplished by column chromatography on silica gel using a gradient elution (20–50% EtOAc in hexanes). 5,5′-Dicyanocresolphthalein: m.p. 140–142 °C (softens); R_f = 0.25 (1:1 C_6H_{14}/EtOAc); ^{1}HNMR ($CDCl_3$): 2.25 (*s*, 6H), 7.20 (*d*, *J* = 2.0 Hz, 2H), 7.28 (*d*, *J* = 2.0 Hz, 2H), 7.49 (*d*, *J* = 7.7 Hz, 1H), 7.64 (*dd*, *J* = 7.4, 7.8 Hz, 1H), 7.78 (*dd*, *J* = 7.4, 7.7 Hz, 1H), 7.99 (*d*, *J* = 7.8 Hz, 1H); ^{13}CNMR ($CDCl_3$) 16.5, 89.9, 99.2, 116.4, 123.9, 125.4, 126.8, 127.6, 128.6, 130.3, 132.9, 134.7, 135.1, 150.7, 157.6, 169.3. Anal. Calcd. for $C_{24}H_{16}N_2O_4{\cdot}(H_2O)_{1.3}$: C, 68.66; H, 4.47, N, 6.67. Found: C, 68.66; H, 4.34, N, 6.44.

4.2.3. 5-Bromo-5′-cyanocresolphthalein

This compound was isolated from the column chromatography above as a side product in the dicyanation reaction: m.p. 240–242 °C; R_f = 0.40 (1:1 C_6H_{14}/EtOAc); ^{1}HNMR ($CDCl_3$): 2.17 (*s*, 3H), 2.18 (*s*, 3H), 6.91 (*d*, *J* = 1.6 Hz, 1H), 7.14 (*d*, *J* = 2.2 Hz, 1H), 7.16 (*d*, *J* = 2.2 Hz, 1H), 7.25 (*d*, *J* = 1.6 Hz, 1H), 7.44 (*d*, *J* = 7.7 Hz, 1H), 7.54 (*dd*, *J* = 7.5, 7.6 Hz, 1H), 7.69 (*dd*, *J* = 7.5, 7.7 Hz, 1H), 7.90 (*d*, *J* = 7.6 Hz, 1H); ^{13}CNMR ($CDCl_3$): 16.4, 17.1, 90.1, 99, 110.3, 116.4, 123.9, 125.4, 126.6, 126.6, 127.1, 128, 128.6, 129.2, 130.1, 133.1, 133.6, 134.8, 134.9, 151.1, 151.1, 157.3, 169.4. Anal. Calcd. for $C_{23}H_{16}BrNO_4$: C, 61.35; H, 3.58, N, 3.11. Found: C, 61.35; H, 3.54, N, 3.08.

4.2.4. 5,5′-Dicarbomethoxycresolphthalein

Dicyanocresolphthalein (3.80 g, 9.59 mmol) is heated for 1 day at gentle reflux in 30% methanolic H_2SO_4 (400 ml). The reaction mixture is allowed to cool, and then it is poured into rapidly stirring ice water. The solid is collected by suction filtration, washed with water, and air-dried. The solid is dissolved in cold methanolic KOH (1%, 500 ml), and the mixture is stirred in an ice-bath for 15 min. The mixture is filtered by gravity, and the insoluble material is discarded. The filtrate is treated with the following and filtered after each step: 5% aq. AcOH (10 ml), 5% aq. AcOH (10 ml), 20% aq. HOAc (500 ml). The insoluble materials are combined, washed with water and dried leaving 2.04 g (4.41 mmol, 46%) of the dicarboxymethyl product, m.p. 270–272 °C; R_f = 0.72 (1:1 C_6H_{14}/EtOAc); ^{1}HNMR ($CDCl_3$): 2.14 (*s*, 6H), 3.82 (*s*, 6H), 7.17 (*d*, *J* = 2.3 Hz, 2H), 7.48 (*d*, *J* = 7.7 Hz, 1H), 7.51 (*dd*, *J* = 7.5, 7.7 Hz, 1H), 7.55 (*d*, *J* = 2.3 Hz, 2H), 7.66 (*dd*, *J* = 7.5, 7.6 Hz, 1H). 7.89 (*d*, *J* = 7.4 Hz, 1H), 11.07 (*s*, 2H); ^{13}CNMR ($CDCl_3$) 16.2, 52.7, 91.2, 111.4, 123.9, 124.0, 125.6, 125.8, 126.4, 127.7, 129.7, 130.9, 134.5, 135.2, 151.8, 160.5, 170.7. Anal. Calcd. for $C_{26}H_{22}O_8{\cdot}(H_2O)_{1.0}$: C, 65.00; H, 5.03. Found: C, 64.78; H, 4.71.

4.2.5. 5-Bromo-5′-carbomethoxycresolphthalein

5-Bromo-5′-cyanocresolphthalein (480 mg, 1.07 mmol) is heated for 3 h at gentle reflux in 30% methanolic H_2SO_4 (100 ml). The reaction mixture is allowed to cool, and the precipitate is collected on a sintered glass funnel with suction and washed with water. The solid is dried in vacuo giving 210 mg (41%), m.p. 233–235 °C; R_f = 0.37 (3:1 C_6H_{14}/EtOAc); ^{1}HNMR ($CDCl_3$): 2.22 (*s*, 3H), 2.24 (*s*, 3H), 3.90 (*s*, 3H), 5.69 (*s*, 1H), 6.98 (*d*, *J* = 1.6 Hz, 1H), 7.21 (*d*, *J* = 1.6 Hz, 1H), 7.27 (*d*, *J* = 2.4 Hz, 1H), 7.54 (*d*, *J* = 7.6 Hz, 1H), 7.59 (*dd*, *J* = 7.4, 7.7 Hz, 1H), 7.65 (*d*, *J* = 2.4 Hz, 1H), 7.74 (*dd*, *J* = 7.4, 7.6 Hz, 1H), 7.95 (*d*, *J* = 7.7, 2H), 11.14 (s, 1H). (*d*, *J* = 7.4 Hz, 1H), (*s*, 2H); ^{13}CNMR ($CDCl_3$) 16.2, 17.1, 52.7, 90.8, 110.2, 111.4, 124.0, 125.5, 125.8, 126.3, 126.4, 127.7, 128.1, 129.5, 129.7, 130.7, 133.9, 134.6, 135.2, 150.9, 151.8, 160.5, 169.7, 170.7. Anal. Calcd. for $C_{24}H_{19}BrO_6(H_2O)_{0.2}$: C, 59.20; H, 4.02. Found: C, 58.98; H, 3.73.

4.2.6. Cresolphthalein mono-methyl ether

A mixture of cresolphthalein (6.92 g, 20.0 mmol) in DMF (50 ml) is cooled in an ice-water bath while a solution of benzyl trimethyl ammonium methoxide (13.2 g, 40 wt.% in CH_3OH, 29.2 mmol) is added in one portion. Methyl iodide (6.0

g, 42 mmol) is added, and the reaction is capped and stirred at room temperature overnight. The mixture is poured into an ice-cold mixture of 10% aq. NH_4Cl (500 ml), and the solution is extracted with CH_2Cl_2 (3×100 ml). The combined organic layers are washed with water (4×200 ml), dried over $CaCl_2$, and concentrated in vacuo. The residue is covered with 1% aq NaOH (300 ml). The mixture is heated to boiling and filtered by gravity. The filtrated is cooled, and acidified with NH_4Cl (30 g) and AcOH (10 ml) with stirring. The resulting solid is collected by suction filtration and washed with water. The solid is dissolved in ethyl ether (400 ml), and the organic layer is washed repeatedly with cold 1% aq NaOH (100 ml ea) until the aqueous layer is no longer blue. The organic layer is dried over $MgSO_4$, filtered, and concentrated in vacuo. The product is dried on vacuum line giving **11** (2.08 g, 29%), m.p. 136–138 °C; R_f=0.17 (3:1 C_6H_{14}/EtOAc); ^{1}HNMR ($CDCl_3$): 2.02 (*s*, 3H), 2.06 (*s*, 3H), 3.67 (*s*, 3H), 6.60–6.64 (*m*, 3H), 6.65 (*d*, *J*=8.2 Hz, 1H), 6.83 (*d*, *J*=8.2 Hz, 1H), 6.98–6.94 (*m*, 2H), 7.38 (*dd*, *J*=7.3, 7.6 Hz, 1H), 7.41 (*d*, *J*=7.6 Hz, 1H), 7.55 (*dd*, *J*=7.3, 7.4 Hz, 1H), 7.79 (*d*, *J*=7.4 Hz, 1H); ^{13}CNMR ($CDCl_3$) 16.2, 16.5, 55.5, 92.7, 109.5, 114.9, 124.2, 124.5, 125.4, 125.9, 126.0, 126.1, 126.8, 129.2, 129.6, 129.9, 132.4, 132.5, 134.3, 153.1, 154.8, 157.9, 171.0. Anal. Calcd. for $C_{23}H_{20}O_4(H_2O)_{0.2}$: C, 75.98; H, 5.65. Found: C, 75.90; H, 5.60.

4.2.7. 5,5′-Dibromocresolphthalein mono-methyl ether

Cresolphthalein monomethyl ether (3.20 g, 8.88 mmol) is dissolved in CH_2Cl_2 (20 ml). The solution is cooled in an ice-water bath, $FeCl_3{\cdot}(H_2O)_6$ (1.4 g, 5.18 mmol) is added in one portion, and then a solution of Br_2 (6.4 g, 35.6 mmol) in CH_2Cl_2 (20 ml) is added dropwise. The reaction is stirred overnight at room temperature under a $CaCl_2$ drying tube. The mixture is diluted with CH_2Cl_2 (160 ml), washed with cold aq. bisulfite (2%, 100 ml) and cold water (2×100 ml), dried over $CaCl_2$, and concentrated in vacuo. The solid is recrystallized from CH_3OH (190 ml) and $CHCl_3$ (10 ml) giving 12 (2.09 g, 45%), m.p. 240–242 °C; R_f=0.32 (3:1 C_6H_{14}/EtOAc); ^{1}HNMR ($CDCl_3$): 2.18 (*s*, 3H), 2.21 (*s*, 3H), 3.73 (*s*, 3H), 6.92 (*s*, 1H), 7.01 (*s*, 1H), 7.14 (*s*, 1H), 7.23 (*s*, 1H), 7.47 (*d*, *J*=7.5 Hz, 1H), 7.52 (*dd*, *J*=7.3, 7.6 Hz, 1H), 7.67 (*dd*, *J*=7.3, 7.5 Hz, 1H), 7.88 (*d*, *J*=7.6 Hz, 1H); ^{13}CNMR ($CDCl_3$) 17.0, 17.1, 60.4, 90.3, 110.2, 117.6, 124.1, 125.5, 126.4, 126.5, 128.1, 129.2, 129.6, 129.9, 133.4, 133.7, 134.6, 137.7, 151.0, 151.4, 155.8, 169.5. Anal. Calcd. for $C_{23}H_{18}Br_2O_4$: C, 53.31; H, 3.50. Found: C, 53.02; H, 3.37.

4.3. Acidity constant determinations

An aliquot (10–30 ml) of a solution of the dye (4–15 mg) in 100 ml of 50 wt.% aq. CH_3CH_2OH is transferred to a thermostated beaker maintained at 25.0 °C. The solution is diluted as necessary 50 wt.% aq. CH_3CH_2OH so that the absorbance reading does not exceed 1.5 throughout the titration. A pinch (50 mg) of NaCl is added to stabilize the pH meter. The solution is recirculated between the beaker and a quartz cuvette by a peristaltic pump. The absorbances are measured with an Ocean Optics CHEM2000 UV spectrometer using a CCD detector. The entire volume of the flow-through system is 6.5 ml. A Fisher Accumet 10 pH meter equipped with a Ag/AgCl pH electrode is calibrated with TRIS/TRIS-HCL (0.05 *m* ea, pa_H 7.85) [19] and KHP (0.05 *m*, pa_H 5.19) [19] before each titration. The probe is kept immersed in the solution throughout the titration. The system is allowed to equilibrate for 1 min after each addition of KOH solution before the absorbances are recorded. The data is corrected for volume changes. Inflection points are determined by fitting the absorption vs pH data to a third order polynomial and then setting the second derivative to zero.

4.4. Molecular modeling

AM1 calculations were carried out using AMPAC version 6.7 available from Semichem, Inc. Optimization was done using the TRUST algorithm with a RMS gradient norm tolerance of 0.1. Solvation energies were calculated with the SM5.2 model. Uv/vis absorptions were calculated from optimized AM1-SM5.2 structures using AMPAC's C.I. routine employing at least 24 levels and at least 12 states.

Acknowledgements

This work was supported by a grant from the National Institutes of Health.

References

[1] Bányai EV. In: Bishop E, editor. Indicators. Oxford: Pergamon Press, 1972: p. 65–176.
[2] Green FJ. The sigma-aldrich handbook of stains, dyes and indicators. Milwaukee: Aldrich Chemical Company; 1990.
[3] Kunimoto K-K, Sugiura H, Kato T, Senda H, Kuwae A, Hanai K. Spectrochim Acta Part A 2001;57:265.
[4] Ozeki T, Morikawa H, Kihara H. Computer aided innovation new mater 2. In: Doyama M, Kihara J, Tanaka M, Yamamoto R, editors. Proc Int Conf Exhib Comput Appl Mater Mol Sci Eng. 2nd. Amsterdam: North-Holland; 1993. p. 925–30.
[5] Berger S. Tetrahedron 1981;37:1607.
[6] Tamura Z, Abe S, Ito K, Maeda M. Anal Sci 1996;12:927.
[7] Maligres PE, Waters MS, Fleitz F, Askin D. Tetrahedron Lett 1999;40:8193.
[8] Ellis GP, Romney-Alexander TM. Chem Rev 1987;87:779.
[9] Taguchi K. J Chem Soc Perkin Trans 1992;2:17.
[10] Taguchi K. J Am Chem Soc 1986;108:2705.
[11] Yoshida N, Shirai T, Fujimoto M. Carbohydrate Res 1989;192:291.
[12] Buvári A, Barcza L. J Chem Soc Perkin Trans 1988; 2:1687.
[13] Tamura Z, Terada R, Ohno K, Maeda M. Anal Sci 1999; 15:339.
[14] Crisponi G, Casu M, Nurchi VM, Cesare-Marincola F, Tivetta T, Silvagni R. Talanta 2002;56:441.
[15] Hawkins GD, Cramer CJ, Truhlar DG. J Phys Chem B 1998;102:3257.
[16] El-Shafei A, Hinks D, Freeman HS, Lye J. AATTCC Review (2001) 2001;1:23.
[17] Barber HJ. J Chem Soc 1943:79.
[18] Barcza L, Buvári-Barcza A. Carbohydrate Res 1989; 192:103.
[19] White Jr DR, Warner PJ. Chem Eng Data 1988;33:174.