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Inhibition of Quinone−Imine Dye Deamination by Complexation with Para-Sulfonated Calixarenes

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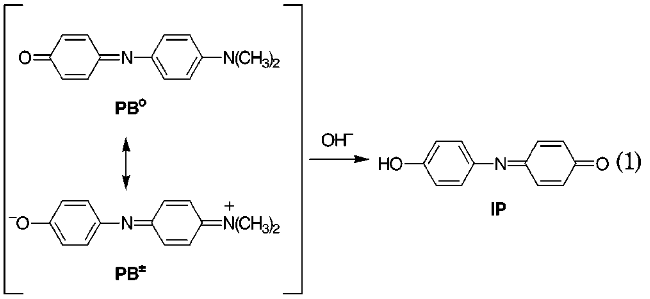
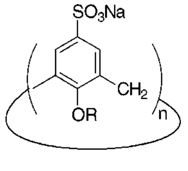
Introduction

It is well-known that formation of inclusion complexes generally induces changes in the chemical and/or physical properties of guest species. Calixarenes, cyclic para-substituted phenols/formaldehyde condensates, have received increasing attention over the past decades owing to their ability to include organic and inorganic compounds and, hence, to modify the properties of a large variety of guest species.[1−3]

In an attempt to improve our understanding of the driving forces leading to complexation by water-soluble calixarenes, we carried out a thermodynamic study on complex formation between 4-[[4-(dimethylamino)phenyl]-imino]-2,5-cyclohexadien-1-one (phenol blue, **PB**) and a series of para-sulfonated calixarenes.[4] During these investigations, it was noticed that the stability of **PB** in aqueous solutions at pH >11 increased significantly in the presence of calixarenes. **PB** (which can be represented by the two resonance forms **PB**$^{\mathbf{O}}$ and **PB**$^{\pm}$, eq 1) is known to be unstable in alkaline solutions;[5] under basic conditions the polar dimethylamino group is readily replaced by oxygen to form 4-[4-hydroxyphenylimino]-2,5-cyclohexadien-1-one (indophenol, **IP**). Even though several reports refer to this chemical transformation, the understanding is only qualitative.[5,6] Quinone−imine dyes such as **PB** are commonly used as redox indicators;[5] in addition, **PB** is widely used as a solvent polarity indicator.[7] Thus, to avoid misinterpretations as a result of the (facile) conversion of **PB** into **IP**, quantitative data on **PB** stability/reactivity are essential.



To analyze the effect of calixarene complexation on **PB** reactivity, the conversion of **PB** into **IP** was studied in aqueous solution at 12 < pH < 13 in the presence of para-sulfonated calixarenes **SC**. The results of such a study are reported here.



Host	n	R
a	4	H
b	6	H
c	6	CH_3

SC

Results and Discussion

The conversion of **PB** into **IP** (and *N*,*N*-dimethylamine) in basic aqueous solution was confirmed by means of ^{1}H NMR spectroscopy. The reaction can be easily followed by UV−vis spectroscopy (Figure 1). The corresponding spectra are characterized by (i) a hypsochromic (blue) shift of the wavelength of maximum absorption (λ_{max}) in the visible region and (ii) clearly defined isosbestic points. Similar characteristics are observed in the presence of **SC** (Figure 2 is representative), although in this case it is also evident that **PB** is initially present in its complexed form. It is well-known that **PB** forms 1:1 complexes with **SC**.[4,8−10] Complexation with **SC** induces a bathochromic (red) shift of λ_{max} and an increase in the absorptivity of **PB**, which are indicative of a reaction field more polar than water as a result of specific host−guest interactions interpreted according to the inclusion model depicted in Figure 3.[9,10] It has been reported that **SCa** and **SCb** have, respectively, three and four weakly acidic OH groups (i.e., pK_a > 11).[11,12] Hence, one would infer that under the experimental conditions of this study (i.e., 12 < pH < 13) a pair (at least) of OH groups on the lower rim of **SCa,b** will be deprotonated. This process, however, does not seem to prevent the formation of **SC** complexes with **PB**.

The spectra obtained upon complete conversion of **PB** into **IP** in the absence and in the presence of **SC** are all identical, which implies that either **IP** does not form complexes with **SC** or, if it does, the differences in extinction coefficient and λ_{max} between the free and complexed forms are negligible.

Rates of conversion of **PB** into **IP** were determined by monitoring the signal growth at 630 nm and are found to follow first-order kinetics in all cases. The observed first-order rate constants (Tables S1)[13] show a linear

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[13] See the Supporting Information.

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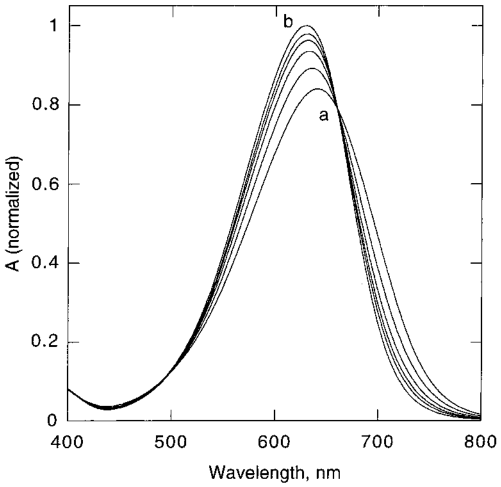


Figure 1. Time-resolved absorption spectra for transformation of **PB** into **IP** in 0.0256 N NaOH aqueous solution at 25 °C, obtained within 1 min (a) and 29 min (b) after sample preparation.

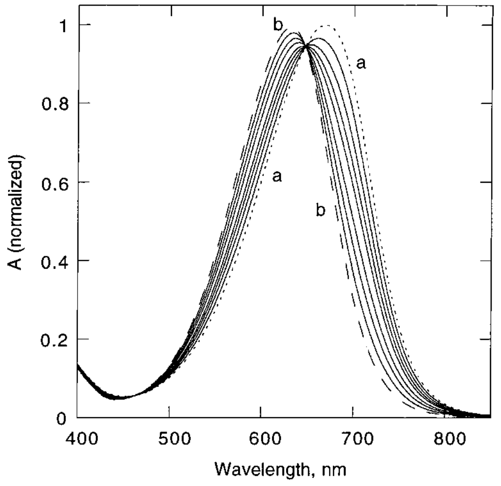


Figure 2. Time-resolved absorption spectra for transformation of **PB** into **IP** in 0.0256 N NaOH aqueous solution in the presence of 5 mM **SCb** at 25 °C, obtained within 1 min (a) and 31 min (b) after sample preparation.

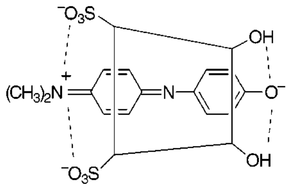


Figure 3. Model for **PB**/para-sulfonated calixarene inclusion complex.[9,10]

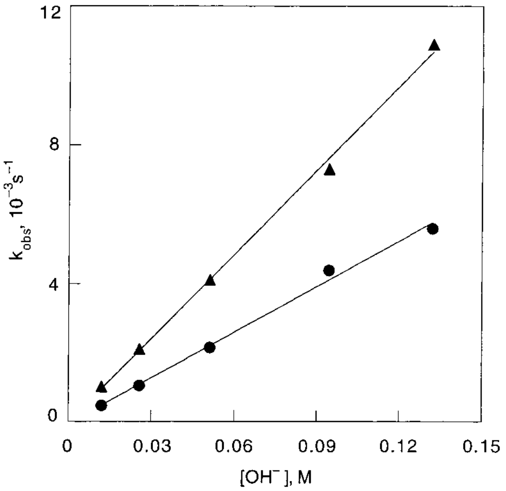


Figure 4. Plots of k_{obs} vs $[OH^-]$ for transformation of **PB** into **IP** in aqueous solution in the absence (▲) and in the presence (●) of 5 mM **SCb** at 25 °C.

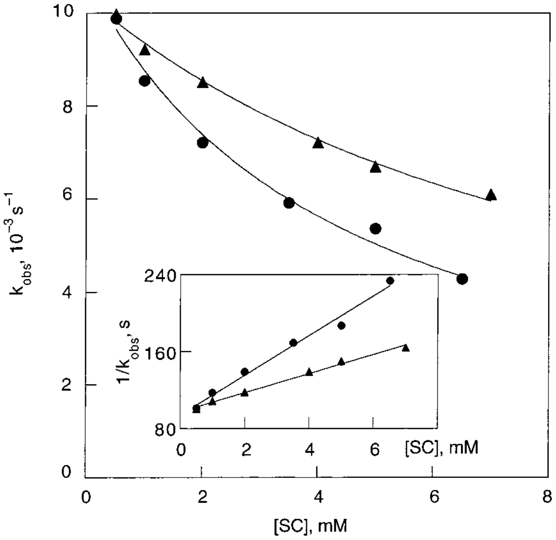


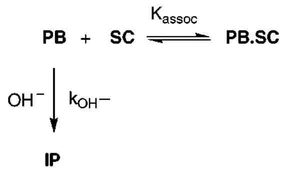
Figure 5. Plots of k_{obs} vs para-sulfonated calixarene concentration for transformation of **PB** into **IP** in 0.132 N NaOH aqueous solution in the presence of **SCa** (▲) and **SCb** (●) at 25 °C. Inset: plots of $1/k_{obs}$ vs para-sulfonated calixarene concentration.

dependence on hydroxide concentration (Figure 4 is representative). The second-order rate constant for hydroxide-catalyzed deamination of **PB** in aqueous solution, namely (8.1 ± 0.1) × 10^{-2} M^{-1} s^{-1}, decreases significantly in the presence of **SC**. The resulting second-order catalytic rate constants are (4.9 ± 0.2) × 10^{-2}, (4.2 ± 0.1) × 10^{-2}, and (4.4 ± 0.2) × 10^{-2} M^{-1} s^{-1} for **SCa** (7 mM), **SCb** (5 mM), and **SCc** (15 mM), respectively. The concentrations of para-sulfonated calixarenes **SC** employed in these series were chosen based on the association equilibrium constants previously reported,[4] which increase in the order **SCc** < **SCa** < **SCb**. In addition, rate constants for hydroxide-catalyzed deamination of **PB** were measured in the presence of sodium 4-hydroxybenzenesulfonate (Table S1),[13] which was employed as model monomer of hosts **SCa,b**. Practically no difference with respect to the values obtained in aqueous solution could be detected, which clearly indicates that the inhibition observed in the presence of **SC** must be due to specific host/guest interactions.

PB deamination was also studied in 0.132 N NaOH aqueous solution in the presence of varying amounts of para-sulfonated calixarenes **SCa,b**. It is found that the observed rate constants (Table S2)[13] decrease nonlinearly as the host concentration increases (Figure 5). This nonlinear dependence is interpreted according to the mechanism shown in Scheme 1, where K_{assoc} and k_{OH^-} represent the association equilibrium constant and the second-order rate constant for hydroxide-catalyzed deamination of **PB**, respectively.

According to Scheme 1, it is assumed that the reactivity of complexed **PB** toward deamination is negligible with

Scheme 1



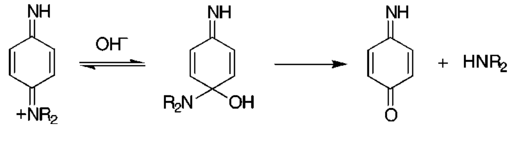
respect to the reactivity of free **PB**. Thus, the observed rate constant (k_{obs}) for the conversion of **PB** into **IP** is given by eq 2:[14]

$$k_{\mathrm{obs}} = \frac{k_{\mathrm{OH}^-}[\mathrm{OH}^-]}{1 + K_{\mathrm{assoc}}[\mathbf{SC}]_{\mathrm{o}}} \qquad (2)$$

Nonlinear fittings of k_{obs} vs $[\mathbf{SC}]_{\mathrm{o}}$ data lead to k_{OH^-} values of (7.80 ± 0.08) and (8.1 ± 0.2) × 10^{-2} $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ and K_{assoc} values of (105 ± 6) and (230 ± 20) M^{-1} for **SCa** and **SCb**, respectively. The former values are in excellent agreement with the second-order rate constant obtained in aqueous solution in the absence of **SC** as described above. Moreover, plots of $1/k_{\mathrm{obs}}$ vs $[\mathbf{SC}]_{\mathrm{o}}$ are fairly linear (Figure 5 inset), which supports the assumption that the reactivity of complexed **PB** is indeed negligible (i.e., ($k^{\mathrm{SC}}_{\mathrm{OH}^-} K_{\mathrm{assoc}}[\mathbf{SC}]_{\mathrm{o}} \leq 0.1 k_{\mathrm{OH}^-}$).[14] According to eq 2, the slope/intercept ratio obtained from the linear $1/k_{\mathrm{obs}}$ vs $[\mathbf{SC}]_{\mathrm{o}}$ plots yields K_{assoc} values for complexation of **PB** in aqueous solutions at pH 13 and 25 °C. The values thus obtained are (100 ± 6) and (220 ± 20) M^{-1} for **SCa** and **SCb**, respectively, and are in excellent agreement with those obtained from the nonlinear fittings. It is noticed that these K_{assoc} values are somewhat lower that those previously obtained at pH 9.00 (0.05 M Borax buffer) and 20 °C, namely (262 ± 6) and (491 ± 8) M^{-1} for **SCa** and **SCb**, respectively.[4] In addition to temperature and type of buffer, the acidity of the phenolic hydrogens on the lower rim of the calixarene cavity is a critical factor which influences binding with guest species. As already mentioned, **SCa** and **SCb** have, respectively, three and four weakly acidic OH groups.[11,12] Thus, the degree of host ionization and, hence, the binding ability will be (quite) different for both series of experiments. Interestingly, regardless of the experimental conditions, the same type of cavity size selectivity is observed, i.e., $K^{\mathbf{SCb}}_{\mathrm{assoc}}/K^{\mathbf{SCa}}_{\mathrm{assoc}} \approx 2$.

According to eq 2, the second-order catalytic rate constants determined in the presence of para-sulfonated calixarenes would correspond to the factor $k_{\mathrm{OH}^-}/(1 + K_{\mathrm{assoc}}[\mathbf{SC}]_{\mathrm{o}})$. An average value of 8 × 10^{-2} $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ for k_{OH^-} leads to K_{assoc} values of ca. 90, 181, and 55 M^{-1} for **SCa**, **SCb**, and **SCc**, respectively, in very good agreement with the K_{assoc} values given in the paragraph above.

The hydroxide-catalyzed elimination of *N*,*N*-dimethylamine from **PB** can be understood in analogy to the mechanism of deamination of quinodiimines (eq 3),[15] albeit the latter are significantly more reactive (e.g., $k_{\mathrm{OH}^-} = 2.5 \times 10^4$ $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ for R = $\mathrm{CH_3}$).[16]



(3)

The inhibition observed as a result of complexation with **SC** is attributed to electronic repulsion between the array of sulfonate groups on the upper rim of the calixarene cavity and the reacting hydroxide ions, which limits the accessibility of the latter to the guest **PB**. This interpretation is in agreement with the remarkable stabilization of arenediazonium ions observed upon complexation with para-sulfonated calixarenes, explained by the strong anionic reaction field resulting from the circularly arranged $\mathrm{SO_3}^-$ groups on the edge of the host cavity.[17] Taking into account (i) the good agreement between the observed rate constants and eq 2 (from which we infer that ($k^{\mathrm{SC}}_{\mathrm{OH}^-} K_{\mathrm{assoc}}[\mathbf{SC}]_{\mathrm{o}} \leq 0.1 k_{\mathrm{OH}^-}$)[14] and (ii) that the product $K_{\mathrm{assoc}}[\mathbf{SC}]_{\mathrm{o}}$ equals ca. 1 for all three para-sulfonated calixarenes at the highest concentrations employed in this study, it follows that complexation by **SC** causes at least a 10-fold decrease in the reactivity of **PB** toward hydroxide-catalyzed elimination of *N*,*N*-dimethylamine.

Experimental Section

Phenol Blue and sodium 4-hydroxybenzenesulfonate (Aldrich) were used as received; their identity was checked by means of ^{1}H NMR spectroscopy. Para-sulfonated calixarenes were prepared from *p-tert*-butylcalixarenes (Aldrich) according to methods described in the literature[9,18,19] in 60−80% yields;[20] their identity and purity were checked by means of ^{1}H NMR spectroscopy and elemental analysis.[20] 1,4-Dioxane (BDH, ACS grade) was fractionally distilled before use. Aqueous solutions were prepared using analytical grade chemicals (BDH) and water purified by passage through a Millipore apparatus.

All reactions were carried out under pseudo-first-order conditions and followed until at least 80−90% conversion of the starting material was observed. Typical substrate (**PB**) concentrations were in the order of 3 × 10^{-5} M. The ionic strength was kept constant at 0.2 M using KCl as compensating electrolyte. All measurements were carried out at (25.0 ± 0.1) °C. Curve fittings were carried out using the general curve fitting procedure of Kaleidagraph software (version 3.0.5) from Abelbeck Software.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council (NSERC) of Canada is gratefully acknowledged.

Supporting Information Available: Observed rate constants for hydroxide-catalyzed deamination of **PB** in aqueous solution in the absence and in the presence of para-sulfonated calixarenes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) If the second-order rate constant for hydroxide-catalyzed deamination of **PB.SC** (i.e., $k^{\mathrm{SC}}_{\mathrm{OH}^-}$) were to be taken into account, k_{obs} would be given by

$$k_{\mathrm{obs}} = \frac{[\mathrm{OH}^-](k_{\mathrm{OH}^-} + k^{\mathrm{SC}}_{\mathrm{OH}^-} K_{\mathrm{assoc}}[\mathbf{SC}]_{\mathrm{o}})}{1 + K_{\mathrm{assoc}}[\mathbf{SC}]_{\mathrm{o}}}$$

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