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LETTERS

Photon-Controlled Phase Partitioning of Spiropyrans

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The reversible partitioning of molecules between immiscible phases, such as in solvent extraction, is usually controlled by chemical composition of one or both phases, temperature, or pH. An additional means for controlling the equilibrium distribution of a solute between phases, the use of light and suitable photochromic molecules, such as those drawn from the spiropyran family, is described. Partitioning of 1′,3′,3′-trimethyl-6-nitrospiro[2*H*-1]-benzopyran-2,2′ indoline (1′-methyl 6-NO_2 BIPS) and its derivatives between toluene and water phases is shown to be controlled by the wavelength of incident light, the ionogenic functional groups on the molecule, and the aqueous solution pH. At pH 2, both 1′-methyl 6-NO_2 BIPS and 1′-(3-carbomethoxypropyl) 6-NO_2 BIPS partition reversibly and preferentially into the aqueous phase when irradiated with ultraviolet light in the 365−370 nm region but only slightly into the aqueous phase when illuminated with wavelengths greater than or equal to 480 nm. The partition coefficient of these spiropyrans at pH 2 and under irradiation with ultraviolet light is 25 times larger than when irradiated with visible light. For aqueous solutions of 1′-(3-carboxypropyl) 6-NO_2 BIPS, the partition coefficient at pH 4 and under UV light irradiation is 22 times larger than that under visible light irradiation, whereas at pH 6 the partition coefficient under UV irradiation is only 2 times greater than under visible light irradiation. These partition coefficient variations are explained by applying chemical equilibrium theory to the reversible, irradiation-induced structural changes in spiropyran molecules. The fit of theory to the data confirms the importance of interface speciation.

Introduction

Photochromism, the reversible change in optical absorbance induced by irradiation with different wavelengths of light, often occurs by photoisomerization of a dissolved organic compound. Of particular utility are the class of molecules known as spiropyrans. When dissolved in nonpolar solvents in the dark, or when exposed to visible light, the majority of spiropyrans are colorless or nearly so in the visible.[1,2] Under these conditions the spiropyran exists in a nonpolar or "closed" spiro form that absorbs light predominantly in the ultraviolet region (Figure 1). When exposed to UV light, the spiropyran undergoes an isomerization wherein the spiro linkage is severed, resulting in a highly polar "open" form that is colored (typically absorbing near 530 nm). As shown in Figure 1, the structure of this open form is a resonance hybrid between a zwitterion and a neutral quinonoid. The zwitterionic form contributes significantly to

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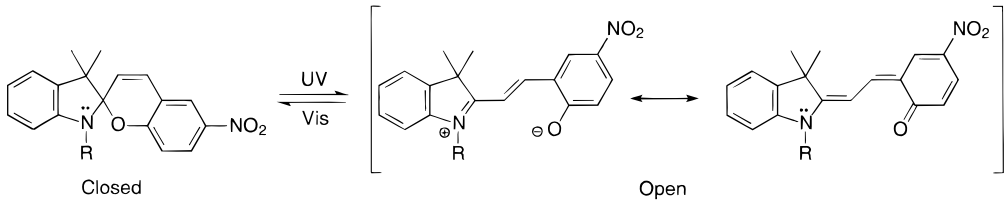

Figure 1. Molecular structures of spiropyran (BIPS) in the closed and open forms. In the "open form" zwitterionic and neutral resonance forms contribute to the structure.

the structure of the open form because the aromaticity of the oxygen-bearing ring is lost in the neutral form.

Most open spiropyrans revert thermally to the closed form in a few minutes or hours. Irradiation of the open form at wavelengths near 530 nm also leads to reversion to the closed form. Thus, spiropyrans may be switched from closed to open forms with UV light, and from open to closed forms with visible light.

Spiropyrans can withstand repeated light-induced cycling between open and closed forms (up to 30 000 in certain cases). They show good quantum yields (between 10% and 50%) for interconversion. They do not generate free radicals as their primary photo product, unlike many photochemically active molecules.

Spiropyrans in their closed form are soluble in a wide range of organic solvents and generally have quite low water solubilities. This behavior has attracted a great deal of interest for their use in light-sensitive optical eyeware,[3−11] although other novel applications have been considered, including optical image storage and light intensity sensors. There has also been some interest in their possible use as chemical separation agents. Metal ions can be extracted from aqueous solution using organic liquid membranes into which spiropyrans are dissolved.[12−14] These chelation extractions have been shown to be photoreversible. Sunamoto and Ino[15,16] have demonstrated that photons can be used to modulate the transport of amino acids across spiropyran-containing lipid bilayers. Other applications explored include conjugation of spiropyrans to electrodes,[17] proteins,[18] and cyclodextrins[19] for use as sensors.

Not studied to date is the reversible, light-modulated equilibrium partitioning of spiropyrans between an organic solvent and water. Interest in this phenomenon arises because it provides a means to change an aqueous solution composition during extraction with no change in temperature and without addition of any auxiliary chemicals. For this application, it is very important to understand the role of ionogenic functional groups—both those present as substituents and those created during photoisomerization—in dictating the spiropyran equilibrium partition coefficient.

Methods and Materials

Synthesis. *1-(3-Carbomethoxypropyl)-3,3-dimethyl-2-methyleneindoline.* A solution of 2,3,3-trimethylindolenine (8.78 g, 0.0547 mol) and methyl 4-bromobutyrate (9.90 g, 0.0547 mol) in 20 mL of chloroform was refluxed for 20 h. The solvent was evaporated, and the reddish residue was washed with diethyl ether and recrystallized from a mixture of diethyl ether and methanol (9:1) to give 14.88 g (0.0437 mol, 80% yield) of the desired indoline as the quaternary ammonium salt: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (6 H, s, 3-CH_3), 2.27 (2 H, m, $CH_2CH_2CH_2COOCH_3$), 2.76 (2 H, t, J = 7 Hz, $CH_2CH_2CH_2$-$COOCH_3$), 3.20 (3 H, s, 2-CH_3), 3.67 (3 H, s, $COOCH_3$), 4.92 (2 H, t, J = 8 Hz, $CH_2CH_2CH_2COOCH_3$), 7.5−8.0 (4 H, m, ArH).

1′-(3-Carbomethoxypropyl)-3′,3′-dimethyl-6-nitrospiro[2H-1]-benzopyran-2,2′-indoline. To 1.77 g (10.5 mmol) of 5-nitrosalicylaldehyde in 30 mL of ethanol was slowly added a solution of 3.60 g (10.5 mmol) of the quaternary salt of 1-(3-carbomethoxypropyl)-3, 3-dimethyl-2-methyleneindoline in ethanol. The mixture was refluxed for 6 h. The resultant dark purple mixture was cooled in an ice bath and filtered, and the filter cake was washed with cold ethanol. Three recrystallizations from ethanol gave 1.85 g (4.54 mmol, 43% yield) of 1′-(3-carbomethoxypropyl)-3′,3′-dimethyl-6-nitrospiro[2*H*-1]benzopyran-2,2′-indoline as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, s, 3-CH_3) 1.28 (3H, s, 3-CH_3), 1.91 (2H, m, $CH_2CH_2CH_2COOCH_3$), 2.35 (2H, m, $CH_2CH_2CH_2COOCH_3$), 3.21 (2H, m, $CH_2CH_2CH_2COOCH_3$), 3.63 (3H,s, $COOCH_3$), 5.86 (1H, d, J = 10 Hz, vinyl H), 6.63−7.20 (6H, m, ArH, vinyl H), 8.00−8.03 (2H, m, Ar H); FAB-MS *m*/*z* calcd for $C_{23}H_{24}N_2O_5$ + H 409.1782, obsd 409.1763 $(M + H)^+$.

1′-(3-Carboxypropyl)-3′,3′-dimethyl-6-nitrospiro[2H-1]benzopyran-2,2′-indoline. 1′-(3-Carbomethoxypropyl)-3′,3′-dimethyl-6-nitrospiro[2*H*-1]benzopyran-2,2′-indoline (100 mg, 0.245 mmol) dissolved in 2 mL of tetrahydrofuran was stirred at room temperature for 24 h with an excess of 10% aqueous NaOH. The resulting solution was then acidified with dilute hydrochloric acid and extracted with chloroform. The chloroform was removed from the organic layer by distillation at reduced pressure, and the residue was chromatographed on silica gel (chloroform containing 10% methanol) to yield 90 mg (0.23 mmol) of the desired spiropyran (93% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, s, 3-CH_3), 1.29 (3H, s, 3-CH_3), 1.91 (2H, m, $CH_2CH_2CH_2COOCH_3$), 2.41 (2H, m, $CH_2CH_2CH_2$-$COOCH_3$), 3.22 (2H, m, $CH_2CH_2CH_2COOCH_3$), 5.88 (1H, d, J = 10 Hz, vinyl H), 6.61−7.25 (6 H, m, ArH, vinyl H), 8.0−8.1 (2H, m, ArH), 10.00 (1H, s, COOH); FAB-MS *m*/*z* calcd for $C_{22}H_{22}N_2O_5$ + H 395.1599, obsd 395.1607 $(M + H)^+$.

Photochemical Experiments. Broad-band light was supplied by a 200 W mercury lamp (Oriel). Cutoff filters (365 and 480 nm long-pass) were used to obtain light of ultraviolet and visible wavelengths. A quartz container filled with distilled water was placed between the filtered light source and the two-phase equilibration cell to minimize solution heating from infrared absorption.

The equilibrium spiropyran distribution coefficient was determined using the following procedure. Equal volumes (5 mL) of toluene (reagent grade, E. M. Science) containing 10^{-4}

M spiropyran and an aqueous phase containing distilled water, 0.1 M NaCl (Fischer, enzyme grade), and either HCl or NaOH (Mallinckrodt N.F.) for pH adjustment were contacted in a quartz test tube. The two-phase mixture was simultaneously irradiated and agitated vigorously with a glass stirring rod for 5 min. This time was determined to be sufficient for photoisomerization and liquid-phase mass transfer to take place so that reproducible, time invariant results are observed. The solution temperatures were maintained between 23 and 24 °C.

The first datum taken was under visible light irradiation of the two-phase mixture. The phases were allowed to separate while irradiated, and care was taken to remove only the toluene phase. The toluene phase was then irradiated with visible light to force all the spiropyran species to the closed form. The absorption spectrum of the toluene phase was then recorded from 800 to 290 nm. Control experiments showed that the measuring light in the spectrometer was not strong enough to cause significant isomerization. The spiropyran concentration was determined by comparing the absorbance at 300 nm with that of known reference standards.

After this measurement, the toluene phase was reintroduced to the equilibration cell, and the two-phase mixture was simultaneously agitated vigorously and irradiated with UV light. The spiropyran concentration of the toluene phase was then determined as described above. Cycles of irradiation, sampling, and spiropyran concentration determination were performed in the sequence: (1) VIS; (2) UV; (3) VIS; (4) UV; (5) VIS.

Spiropyran pK_a values were measured by two-phase titrations. For 1′-methyl 6-NO_2 BIPS, a two-phase mixture was prepared by adding 10 mL of 5 mM 1′-methyl 6-NO_2 BIPS in toluene to 10 mL of 0.1 M aqueous NaCl solution in a beaker. The mixture was stirred for 15 s with a hand held glass rod while it was irradiated with UV light. The two layers were allowed to separate for 30 s while still irradiated, and the pH of the aqueous phase was measured with a Corning Premium Rugged Bulb Low Profile electrode incorporating a silver ion barrier internal element and a ceramic junction. The mixture in the beaker was then titrated with 25 mM HCl, using 0.5 mL per addition. After each addition, and under constant irradiation, the mixture was stirred and allowed to phase separate, and the pH was determined as before. A mixture containing no spiropyran was titrated in an identical manner to provide a reference.

Reagent grade glycine was titrated similarly to test the sensitivity and accuracy of the titration method. The titration of 1′-(3-carboxypropyl) 6-NO_2 BIPS was also performed as a two-phase titration under visible light, as described above. The titration temperature for all systems was maintained at 23−24 °C.

Results

Using the experimental procedure described above, the partition coefficient P for 1′-(3-carbomethoxypropyl) 6-NO_2 BIPS at pH 2 was determined under various conditions of illumination and is shown in Figure 2. The partition coefficient is defined in these experiments as the ratio of the equilibrium spiropyran concentration in the aqueous phase to the equilibrium concentration in the toluene phase. Table 1 summarizes the data obtained at pH 2 for both methyl and methyl ester forms of 6-NO_2 BIPS. At pH values of 4, 6, 8, and 10, their partition coefficients are very close to zero under both UV and visible light irradiation.

For 1′-(3-carboxypropyl) 6-NO_2 BIPS, data could only be obtained at pH values of 4 and 6. The absorbance spectra for the carboxyl derivative could not be calibrated reliably at pH values of 2, 8, and 10 since the absorbance increased over time probably due to chemical reactions. The other derivatives were stable at these pH values. The data shown in Table 2 indicate that there is a significant difference in partitioning between the UV and visible light irradiated two-phase equilibrium at pH 4. At pH 6 the difference is less dramatic.

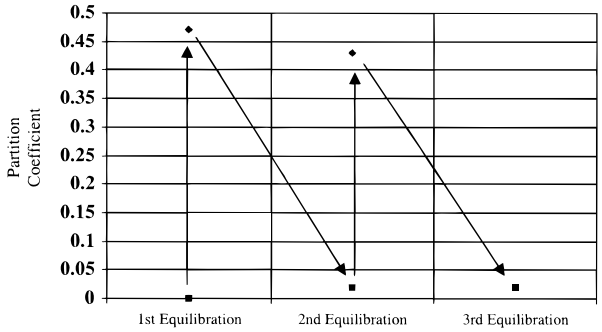

Figure 2. Sequential change in partition coefficient for 1′-(3-carbomethoxypropyl) 6-NO_2 BIPS for a two-phase system where the aqueous solution is pH 2. Dashed lines show the experimental sequence of equilibrations for this system under UV and visible light conditions. Diamonds indicate UV irradiation conditions, while the squares denote irradiation with visible light.

TABLE 1: Partition Coefficients (P) of Two Spiropyrans between Water and Toluene at pH = 2 during a Series of Experiments Where the Wavelength of Light Irradiating the Sample Is Alternated between Visible and UV Ranges

	P = (concentration aqueous)/(concentration toluene)				
compound	VIS	UV	VIS	UV	VIS
1′-methyl 6-NO_2 BIPS	0	0.39	0.09	0.4	0.03
1′-(3-carbomethoxypropyl) 6-NO_2 BIPS	0	0.47	0.02	0.41	0.02

TABLE 2: Partition Coefficients for 1′-(3-Carboxypropyl) 6-NO_2 BIPS at pH Values of 4 and 6 during a Sequence of Experiments Where the Wavelength of Light Irradiating the Sample Is Alternated between Visible and UV Ranges

	1′-(3-carboxypropyl) 6-NO_2 BIPS partition coefficient, P = (concentration aqueous)/(concentration toluene)				
pH	VIS	UV	VIS	UV	VIS
4	0	0.22	0.01	0.27	0.05
6	0.1	0.27	0.1	0.22	0.1

An interpretation of the partitioning data should consider photoisomers of spiropyrans in the open or closed state as well as the pK_a values of the ionogenic groups present. Detailed analysis of the species present when 6-NO_2 BIPS is in the open form[21] and of a related merocyanine compound[20] (which is similar to the open form of BIPS) illustrates the importance of considering the contributions of the two resonance forms to the pK_a values of the ionogenic groups. (The "open form" referred to here is most likely a rapidly equilibrating mixture of several conformational isosmers.) For the open form of BIPS and the merocyanine, there is a charge-separated resonance form featuring quarternary amine and phenolate groups and a quinoid, uncharged resonance form (Figure 1).[20,21] The carboxyl derivative of 6-NO_2 BIPS has, in addition, another ionogenic group that is expected to have a pK_a value similar to the pK_a of the carboxylic acid group of 4-aminobutyric acid.

Hall et al.[20] have shown that the pK_a value (5.0) of the phenolic group on the merocyanine (which lacks the nitro group) is much lower than the pK_a of phenol (9.9). They attribute this dramatic increase in acidity to the surface potential of merocyanine at the air−water interface and the presence of the

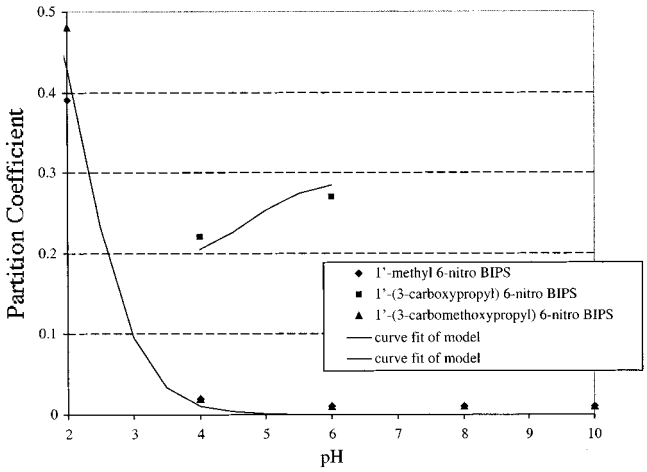

Figure 3. Partitioning of the open form of spiropyrans between toluene and water as a function of the aqueous-phase pH. Curves are predictions based on acidities of phenolate and carboxyl groups. The closed forms of 1′-methyl and 1′-(3-carbomethoxypropyl) 6-NO_2 BIPS have partition coefficients of about 0.02 at these pH values. The 1′-(3-carbomethoxypropyl) 6-NO_2 BIPS derivative is unstable at pH 2, 8, and 10. The partition coefficient of the closed form is only 0.01 at pH 4 (pK_a of the carboxylic acid group is about 3.5). At pH 6, the closed form has a partition coefficient of about 0.1.

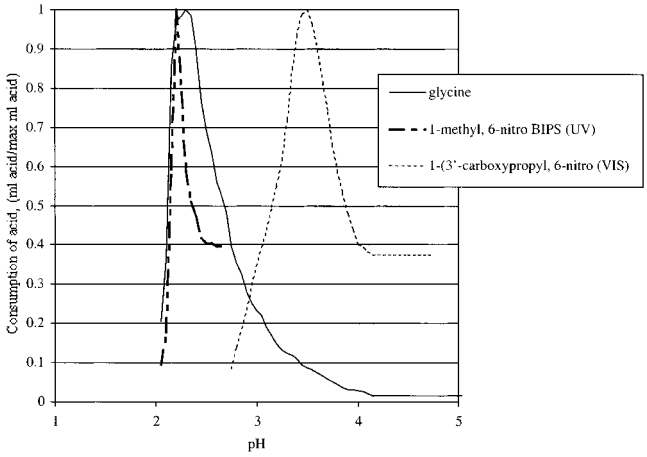

Figure 4. Titration results at 23 °C for glycine, 1′-methyl 6-NO_2 BIPS under UV irradiation, and 1′-(3-carboxypropyl) 6-NO_2 BIPS under visible irradiation. All three titrations were done using a two-phase system of toluene and water. Blank titrations with no solute were obtained simultaneously under the same irradiation and two-phase conditions in order to directly measure the amount of HCl consumed during the titration. The pK_a value of glycine determined through experimentation was 2.3. For 1′-methyl 6-NO_2 BIPS, a pK_a of 2.2 was determined for the phenolate group present when the molecule is in the open form due to UV irradiation. For 1′-(3-carboxypropyl) 6-NO_2 BIPS under visible light (to keep it in the closed form) the carboxylic acid substituent was found to have a pK_a of 3.5.

quinoidal resonance contribution, which serves to stabilize the unprotonated form. On the basis of this information and using the well-known fact that a nitro group increases the acidity of phenol from a pK_a of 9.9 to 7.15,[22] the pK_a of the phenolic group of the open form of 6-NO_2 BIPS can be estimated to be 2.25 using linear free energy relationships.[22]

To test this hypothesis, a two-phase acid titration of 1′-methyl 6-NO_2 BIPS was performed while the system was irradiated under UV light. Figure 4 shows the HCl titration results determined for glycine, UV-irradiated 1′-methyl 6-NO_2 BIPS, and visible-irradiated 1′-(3-carboxypropyl) 6-NO_2 BIPS. In Figure 4, the pH of the aqueous phase is plotted against a relative scale of acid consumed. Blank titrations were performed for both systems to determine the volume of standardized HCl consumed without a dissolved solute. In Figure 4, the pK_a value is determined at the pH where the maximum difference exists between the consumption of acid for the two-phase system when a solute is present versus the blank titration. For the purposes of graphing the data for glycine and the spiropyrans, the ordinate is a relative scale since different total solute concentrations were used. The pK_a of glycine using our method (2.3) compares very well with the published value (2.35). The pK_a of 2.2 measured for 1′-methyl 6-NO_2 BIPS is in excellent agreement with the estimate of 2.25 derived from linear free energy relationships.

To determine the acidity of the carboxylic acid substituent of 1′-(3-carboxypropyl) 6-NO_2 BIPS, an acid titration was performed under visible light to maintain the molecule in its closed form. This titration yields a pK_a value of 3.5, which is very close to the value of 4.0 for a similarly amine-substituted carboxylic acid, 4-aminobutyric acid.

The following simplified sequence of phase-transfer equilibria is proposed to interpret the partitioning of the open form of spiropyran (with no added ionogenic side groups) between toluene and water.

$$S^{\pm}_{tol} \rightleftarrows S^{\pm}_{i} + H^{+}_{i} \rightleftarrows SH^{+}_{aq}$$

In the toluene phase, the spiropyran is in the open form ($S^{\pm}$, Figure 1) after UV irradiation. However, at the interphase region between toluene and water (denoted by subscript i), the spiropyran can be protonated at the phenolate functional group. The resulting species with a net positive charge readily transfers to the aqueous phase. The water solubility of the closed spiropyran is assumed to be negligible.

The mathematical equation describing the apparent partition coefficient is This equation assumes that the partition coefficient

$$P_{\text{apparent}} = \frac{P_{SH^+}}{1 + 10^{(\text{pH}-\text{p}K_a)}}$$

approaches its maximum value when the pH is much lower than the pK_a of the phenolic group on the spiropyran. Figure 3 shows a prediction of the measured partition coefficient data for the three 6-NO_2 BIPS compounds as a function of pH. The prediction uses a value for the pK_a (phenolic 6-NO_2 BIPS) of 2.2 measured by titration. The value of P_{SH^+} is an adjustable parameter obtained by fitting the data. Using a least-squares fit of the linearized equation with no intercept, $P_{SH^+} = 0.68$ with $r^2 = 0.987$ and $F = 538$.

For the spiropyran containing a carboxylic acid functional group, the equilibria can be represented by the following scheme.

$$S^{+/2-}_{tol} \rightleftarrows S^{+/2-}_{aq} + H^{+}_{aq} \rightleftarrows SH^{\pm}_{i} \rightleftarrows SH^{\pm}_{tol}$$

$$SH^{\pm}_{i} + H^{+}_{i} \rightleftarrows HSH^{+}_{aq}$$

As before, the water solubility of the closed spiropyran is assumed to be negligible. This scheme leads to the following equation for predicting the effect of pH on the partition coefficient of the open form of 1′-(3-carboxypropyl) 6-NO_2 BIPS.

$$P_{\text{app}} = \frac{P_{HSH^+}}{1 + 10^{(\text{pH}-\text{p}K_a)}} + \frac{P_{S^{+/2-}}}{1 + 10^{(\text{p}K_{a,\text{COOH}}-\text{pH})}}$$

The prediction of this equation using the measured pK_a (phenolic 6-NO_2 BIPS) of 2.2 and the measured pK_a (carboxyl) of 3.5 is also shown in Figure 3. Again, the agreement is gratifying. There

are two adjustable parameters, namely P_{HSH^+} and $P_{S^{+/2-}}$. Since there are only two data points, the parameters can be estimated as $P_{HSH^+} = P_{S^{+/2-}} = 0.27$ in order to generate the short curve in Figure 3.

The purpose of developing mathematical models of the partitioning of the open form of spiropyrans is to suggest ways that they can be modified so that the difference between partitioning under UV and visible light irradiation is maximized. The results from the experiments with 1′-(3-carboxypropyl) 6-NO_2 BIPS clearly show that this is possible. At pH 4, the ratio of partition coefficients for UV and visible irradiation is $P_{UV}/P_{vis} = 22$ (Table 2). A ratio of a similar magnitude for 1-methyl 6-NO_2 BIPS and 1′-(3-carbomethoxypropyl) 6-NO_2 BIPS requires solution pH values near 2. If instead an acid substituent weaker than a carboxylic acid were used, the region of large partition coefficient value ratios should continue to shift to pH ranges much nearer neutral, as long as the new acid substituent is relatively hydrophilic.

Conclusions

These experiments have demonstarted that the reversible photoisomerization of spiropyrans in this family can be used to change the equilibrium partition coefficient of molecules between toluene and water. Consideration of ionic equilibria and the impact that surface charges have on changing the acidity of the phenolic oxygen group formed upon UV irradiation yields a mathematical model that predicts partitioning as a function of aqueous solution pH. At pH 2 the partition coefficient of 1′-methyl and 1′-(3-carbomethoxypropyl) 6-NO_2 BIPS between toluene and water shows a 25-fold increase when irradiated with UV light. Attaching a side chain with a carboxyl functional group to the amine of 6-NO_2 BIPS provides a similarly dramatic increase (22-fold) at pH 4. Conversely, the closed form of the carboxylic acid derivative does not have much water solubility, and the partition coefficients at pH values near and below the pK_a of the carboxylic acid functional group are lower. The insights gained from the model and the corroborating experiments suggest that spiropyrans can be designed to yield a marked difference in hydrophobicity between the open and closed forms that depends both upon aqueous-phase pH and the ionogenic groups present in the molecule. The organic solvent properties should also influence the proton affinity of the molecule, thus affecting the spiropyran phase partitioning. Such considerations suggest that with careful molecular engineering one can envision a family of spiropyrans whose partitioning is continuously variable over a large pH range and under the control of light.

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