

### Summary and Conclusion

We have determined rate constants for the DBDO<sup>+</sup> cation system in the fast- and slow-exchange regions and have obtained good agreement between individual experiments. We have also found smaller rate constants and higher activation energies in a lower bulk dielectric constant medium indicating that ion pairing between the organic cation and ClO<sub>4</sub><sup>-</sup> is probable.

Slow-exchange studies have shown that the correction to the slow-exchange equation proposed by Zandstra and Weissman<sup>15</sup> for anion systems also applies to cation systems. The theoretical correction introduced by Johnson and Holz<sup>16</sup> which extends the usefulness of eq 2 has been applied to our fast exchange data and we have found that by applying this correction a lower rate constant was obtained, which is what would be

expected since the *Z* values of several data points did exceed the limiting value.

Thus, we have shown that either eq 1 or 2 is generally valid to determine electron-transfer rate constants if appropriate corrections are made.

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## Kinetics of Proton Transfer to Cyanines.<sup>1</sup> A Temperature-Jump Study

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**Abstract:** A linear free energy type relationship has been obtained between the logarithm of the measured protonation rate constants of a number of substituted 2,2'-cyanines and the change in  $\pi$ -electron delocalization energies as a consequence of protonation. The absolute values of all rate constants measured by the T-jump technique are five to seven orders of magnitude below diffusion controlled indicating that protonation occurs on the methine carbon. Proton-transfer rate constants to the carbon from second acid-base pairs have Brønsted plots that are strongly unsymmetrical about  $\Delta pK = 0$  showing saturation behavior at negative  $\Delta pK$  values. Activation energies for proton transfer to pseudoisocyanine are between 8 and 9 kcal/mol, and entropies of activation are strongly negative leading to relatively low Arrhenius factors. Solvent isotope effects measured as a function of temperature for proton transfer involving acetic acid and pseudoisocyanine are large ( $\sim 6$ ). Kinetic salt effects support our assignment of relaxation times. Measurements in methanol-water solvents of varying dielectric constants suggest that the effective reaction distance for proton transfer may be relatively short. Thermodynamic parameters for proton transfer involving pseudoisocyanine are presented.

The 2,2'-cyanine compounds represent an interesting class of carbon acids whose acidities are known to vary directly as a function of changes in their  $\pi$ -electron delocalization energies<sup>2</sup> resulting from the difference in conjugation between the acid and conjugate base forms. To our knowledge there exists no kinetic study in the literature with respect to proton transfer to and from the methine carbon. The ultimate goal of such a study would be the understanding of the mechanism of proton transfer to aromatic carbon acids and the factors that determine the magnitude of the transfer rate constants. The limiting rates of proton transfer to carbon acids cover a range that is generally below the

diffusion controlled limit characteristic for oxygen and nitrogen acids.<sup>3</sup> The main reasons given for the lowering of the rates of protonation of carbon acids include relatively weak hydrogen bonding between the carbon acceptor site and solvent molecules and the occurrence of molecular and electronic structure changes upon protonation.<sup>3</sup> The 2,2'-cyanines represent systems for which such assertions can be tested directly. Changes in the  $\pi$ -electron energies can be readily achieved by protonation and the electron densities can be calculated by conventional methods. Thus a direct correlation between the calculated polarity of the methine carbon in the substituted compounds and the dynamics of its protonation will be possible.

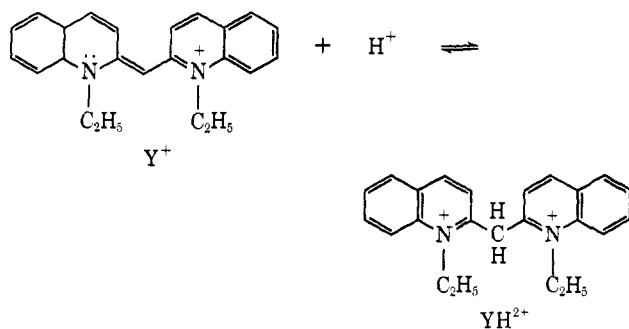
The protonation equilibria of the 2,2'-cyanines can be represented by the example of pseudoisocyanine

(1) (a) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968. (b) In partial fulfillment of the requirements for the M.S. degree of P. J. Dynes, University of Southern California, 1969.

(2) E. Daltrozzo, G. Hohlneicher, and G. Scheibe, *Ber. Bunsenges. Phys. Chem.*, **69**, 190 (1965), and references cited therein.

(3) (a) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964); (b) M. L. Ahrens, M. Eigen, W. Kruse, and G. Maass, *Ber. Bunsenges. Phys. Chem.*, **74**, 382 (1970).

(diethyl-2,2'-cyanine chloride,  $pK_a = 4.04$ )<sup>4</sup> as



Protonation of the middle carbon atom causes  $sp^2$ - $sp^3$  hybridization. The conjugated  $\pi$ -electron system extends over the whole *planar* molecule in the singly charged basic form  $Y^+$  which absorbs in the visible (525 nm), whereas in the doubly charged colorless acid form  $HY^{2+}$  it is interrupted and two separate smaller  $\pi$ -conjugated systems exist. The change in delocalization energy on protonation,  $\Delta G_{loc}$ , is equal to the difference between the  $\pi$ -electron energies of the acid and base forms.<sup>5</sup> A linear energy relationship has been found between the C-H acidity and the change in  $\pi$ -electron delocalization energy for structurally similar dyes of the 2,2'-cyanine type (Figure 1).<sup>2</sup> A further linear relationship characteristic of cyanine dyes which contain quinoline rings is obtained when the frequency of the band center of the longest wavelength band of the conjugate base is plotted *vs.* the experimentally determined  $pK_a$ .<sup>6</sup> The difference between the work for electronic excitation and the overall work for proton binding is constant;<sup>6</sup> *i.e.*, both electronic excitation and proton binding lead to (different) relocation of the  $\pi$  electrons.

The rate of protonation of the C atom is measured at relatively low pH ( $\ll 7$ ) in the absence of a buffer. Rates of proton transfer are measured at near neutral pH in the presence of a second acid-base pair<sup>3,7</sup> such as an O acid. A characteristic relationship between the logarithms of the measured forward and backward proton-transfer rate constants and the  $pK$  difference,  $\Delta pK$ , between the donor and acceptor is obtained. At large  $\Delta pK$  values the proton-transfer rate constant to the stronger acceptor is generally diffusion controlled for O and N acids. At  $\Delta pK = 0$  the two curves intersect. They are expected to be unsymmetrical with respect to each other, if the two acid-base pairs belong to different acid types. For C acids, however, the transition from a slope of  $\alpha = 0$  (where  $\alpha$  is the Brønsted coefficient,  $\partial \log k / \partial \Delta pK$ ) to  $\alpha = 1$  occurs generally over a wider  $\Delta pK$  range than that for the "normal" O and N acids as has been shown, for example, for proton transfer between acetylacetone (keto form) and several bases and between its negative ion and the conjugate acids.<sup>3</sup>

In this study the results of relaxation measurement of a number of 2,2'-cyanines are reported. The relatively low values of the measured protonation rate

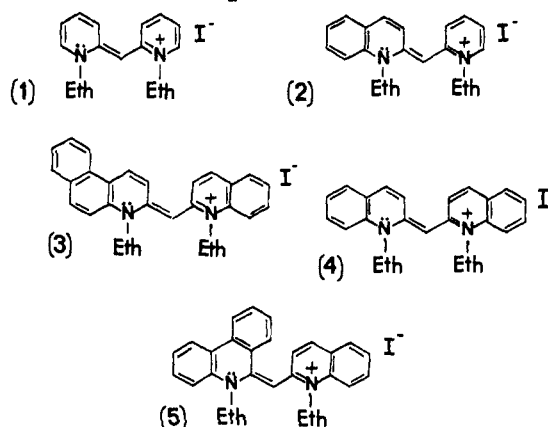
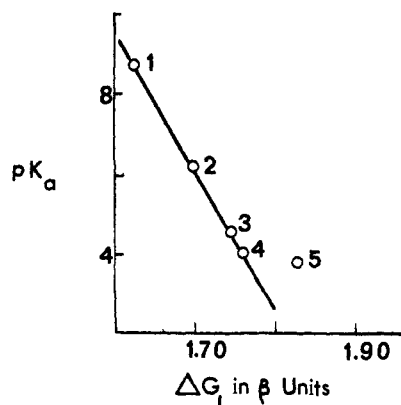


Figure 1.  $pK_a$  of cyanines *vs.* change in  $\pi$ -electron delocalization energy,  $\Delta G_{loc}$ , taken from ref 2: (1) 1,1'-diethyl-2,2'-pyridocyanine, (2) 1,1'-diethyl-2-pyrido-2'-cyanine, (3) 1,1'-diethyl-5,6-benzo-2,2'-cyanine, (4) 1,1'-diethyl-2,2'-cyanine, and (5) 1,1'-diethyl-3,4-benzo-2,2'-cyanine.

constants give further evidence<sup>8</sup> that the proton is transferred to the methine carbon atom rather than to the ring nitrogen. The temperature-jump technique<sup>9</sup> lends itself ideally to the study of the relaxation behavior of the above equilibria, since the cyanines, being present in small concentrations, act as their own indicators. Furthermore, the measured relaxation times are in a time range (upper millisecond region) where optimum conditions of precision of the recording equipment can be achieved.

### Experimental Section

Studied were cyanines 2, 3, 4, 5 (identified in Figure 1), and 6 (6-ethoxy-1,1'-diethyl-2,2'-cyanine iodide,<sup>10</sup>  $pK = 4.74$ ).<sup>4</sup> Second acid-base pairs were of commercially available reagent grade. Deuterium oxide contained 99.8% D. Spectrophotometric  $pK$  determinations were carried out on a Beckman DK-2A spectrophotometer and pH measurements were made on a Beckman Expandomatic pH meter. For  $D_2O$  as solvent the pH meter readings were converted to pD by the relation<sup>11</sup>  $pD = pH + 0.40$ . Potassium nitrate was added to the solutions to provide a constant ionic strength of 0.2. A temperature-jump instrument (Messanlagen Studiengesellschaft, Göttingen) was used to measure relaxation times. The change in intensity of the visible absorption band of

(8) L. H. Feldman, A. H. Herz, and T. H. Regan, *J. Phys. Chem.*, **72**, 2008 (1968).

(9) M. Eigen and L. De Maeyer, "Technique of Organic Chemistry," Vol. VIII, Part II, A. Weissberger, Ed., Interscience, New York, N. Y., 1963.

(10) We thank Dr. W. B. Kendall, Eastman Kodak Research Laboratories, Rochester, N. Y., for a generous gift of cyanines 2, 3, 5, and 6, and Dr. E. Daltrozzo for pseudoisocyanine chloride (cyanine 4).

(11) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

(4) G. Scheibe, W. Seiffert, H. Wengenmayr, and C. Jutz, *Ber. Bunsenges. Phys. Chem.*, **67**, 560 (1963).

(5) A. Streitwieser, *Tetrahedron Lett.*, **6**, 23 (1960).

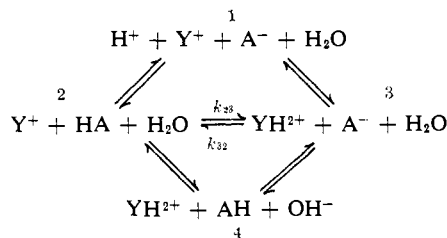
(6) G. Scheibe, *Chimia*, **15**, 10 (1961), and references cited therein.

(7) For a general discussion, see "The Kinetics of Proton Transfer Processes," *Discuss. Faraday Soc.*, **39** (1965).

the cyanine base present in indicator concentration was followed as a function of time after the temperature of the solution was raised by 3.8 to 25.0° within a few microseconds. Signal to noise ratios were between 2000 and 3000.

**Reaction Mechanism.** Proton transfer between the cyanine, its conjugate base, and a second acid-base pair can take place in the presence of water as shown in Scheme I.<sup>3</sup> The upper path 2 ↔

Scheme I



1 ↔ 3 represents protolysis in acid solution, whereas the lower path 2 ↔ 4 ↔ 3 represents hydrolysis in basic solution. For the present cyanine systems it is not permissible at any pH to assume a steady state for states 1 and 4, since the H<sup>+</sup> and OH<sup>-</sup> concentrations become comparable with or exceed the cyanine concentrations. Three relaxation times are predicted for the general mechanism.<sup>3a</sup> However, in acid solution at pH ≪ 7 the hydrolysis path becomes unimportant and only two relaxation times are expected. Since YH<sup>2+</sup> and Y<sup>+</sup> are present in indicator concentrations (~10<sup>-5</sup> M) it can be shown<sup>12</sup> that one of the two relaxation times is due to the rapid equilibration of the added acid-base pair, HA ⇌ H<sup>+</sup> + A<sup>-</sup>, which in the case of O and N acids is much shorter than the second relaxation time involving the "slow" C acid "indicator." Therefore, the "slow" protolysis equilibrium 3 ↔ 1 is measured directly at low pH by following the change in the visible cyanine base absorption as a function of time in the temperature-jump cell while the rapid step 2 ↔ 1 is at equilibrium. As the pH increases the relaxation rate for the cyanine protolysis equilibrium 3 ↔ 1 decreases and it eventually becomes much slower than the ensuing proton transfer 2 ↔ 3. Furthermore, the change in signal due to protonation becomes too small to be detected experimentally at pH > 4.0.

Owing to the relative slowness and pH dependence of the reactions involving the cyanines, their protolysis and proton-transfer equilibria can thus be observed separately and directly, and the otherwise complex rate expressions<sup>3a</sup> simplify considerably as shown in the following.

## Results

**pK<sub>a</sub> of Pseudoisocyanine under Various Conditions.** Our spectrophotometric pK<sub>a</sub> determinations of pseudoisocyanine (cyanine 4) were done at 525 nm at a total cyanine concentration of 1 × 10<sup>-5</sup> M and μ = 0.20 (KNO<sub>3</sub>). Aggregation of dye ions is negligible at the low concentrations employed. The pK<sub>a</sub> has been obtained from

$$\text{pH}_{\text{cor}} = \text{pK}_a + \log \alpha / (1 - \alpha)$$

where α is the degree of dissociation of the protonated cyanine. Plots of log α/(1 - α) vs. pH<sub>cor</sub> were straight lines of slope 1.0. The observed pH was corrected for concentration using an activity coefficient of 0.77. Since temperature corrections for activity coefficients are very small for the present temperature range, they have been neglected. A van't Hoff plot was used to obtain ΔH° for protolysis. Enthalpies of deuteration were determined in a similar manner. The thermodynamic parameters are given in Table I. Individual pK<sub>a</sub> values are found in Tables II, IV, and V. The results of pK<sub>a</sub> determinations in methanol-water solvents are given in Table VIII together with the activity

(12) G. W. Castellan, *Ber. Bunsenges. Phys. Chem.*, **67**, 898 (1963).

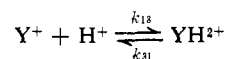
**Table I.** Thermodynamic Parameters for Pseudoisocyanine, μ = 0.20

	ΔG° <sub>25.0°</sub> , kcal/mol	ΔH° <sub>25.0°</sub> , kcal/mol	ΔS° <sub>25.0°</sub> , eu
HY <sup>2+</sup> ⇌ H <sup>+</sup> + Y <sup>+</sup>	5.47	6.32	2.85
DY <sup>2+</sup> ⇌ D <sup>+</sup> + Y <sup>+</sup>	6.26	6.95	2.31
HAc ⇌ H <sup>+</sup> + Ac <sup>-b</sup>	6.15 <sup>a</sup>	-0.10 <sup>a</sup>	-22.1 <sup>a</sup>
DAc ⇌ D <sup>+</sup> + Ac <sup>-</sup>	6.90 <sup>a</sup>	0.28 <sup>a</sup>	-22.2 <sup>a</sup>
HY <sup>2+</sup> + Ac <sup>-</sup> ⇌ HAc + Y <sup>+</sup>	-0.68	6.40	25.0
DY <sup>2+</sup> + Ac <sup>-</sup> ⇌ DAc + Y <sup>+</sup>	-0.64	6.67	24.5

<sup>a</sup> R. Gary, R. G. Bates, and R. A. Robinson, *J. Phys. Chem.*, **69**, 2750 (1965). <sup>b</sup> Ac<sup>-</sup> refers to the acetate ion.

coefficients<sup>13</sup> used. The pK<sub>a</sub> values of cyanines 2, 3, 5, and 6 are those of ref 2.

**Protolysis.** In order to measure the relaxation times for protolysis of the various 2,2'-cyanines, temperature-jump measurements were carried out in unbuffered solutions at sufficiently high H<sup>+</sup> concentrations where small concentration changes of the absorbing conjugate dye base could be detected spectrophotometrically (optical densities < 0.1) as a function of time. Generally the pH of the solutions was adjusted 1.5–2.0 pH units below the pK<sub>a</sub> of the cyanine under study. In the case of cyanine 4 (pseudoisocyanine) whose ε<sub>525</sub> is 7 × 10<sup>4</sup> M<sup>-1</sup> cm<sup>-1</sup> at an ionic strength of 0.25<sup>8</sup> the pH range was 2.5–2.8. Dimerization and especially higher aggregation occur to a negligible extent at the small effective conjugate base concentrations used. Moreover, the relaxation time for dimerization should be of the order of microseconds in which range no relaxation time was detected in our solutions. In the absence of a second acid-base pair the protonation equilibrium 1 ↔ 3 is measured directly at sufficiently low pH



where

$$1/\tau_{13} = k_{13}(\bar{c}_{\text{Y}^+} + \bar{c}_{\text{H}^+}) + k_{31} \quad (1)$$

Since  $\bar{c}_{\text{H}^+} \gg \bar{c}_{\text{Y}^+}$ , eq 1 simplifies to

$$1/\tau_{13} = k_{13}\bar{c}_{\text{H}^+} + k_{31} \quad (2)$$

It is interesting to note that due to the above inequality the absolute equilibrium concentration of Y<sup>+</sup> does not enter into the kinetic expressions.  $\bar{c}_{\text{H}^+}$  is calculated from the hydrogen ion activity as measured by the glass electrode by the use of a mean activity coefficient of 0.77 for μ = 0.20 (KNO<sub>3</sub>).

Kinetic results for cyanine 4 are given for three temperatures in Table II. For every solution one discrete relaxation time was measured. Each reported relaxation time represents an average value of three measurements whose standard deviation was ± 5%. Figure 2 shows a representative plot of 1/τ<sub>13</sub> vs.  $\bar{c}_{\text{H}^+}$  for cyanine 4 at three temperatures. Similar relaxation time measurements were carried out for cyanines 2, 3, 5, and 6. Their corresponding protonation rate constants are summarized in Table III for 25° and μ = 0.2. The kinetic ratios k<sub>31</sub>/k<sub>13</sub> are in good agreement with the corresponding thermodynamic equilibrium

(13) R. G. Bates and R. A. Robinson in "Chemical Physics of Ionic Solutions," B. E. Conway and R. G. Barradas, Ed., Wiley, New York, N. Y., 1966, Chapter 12.

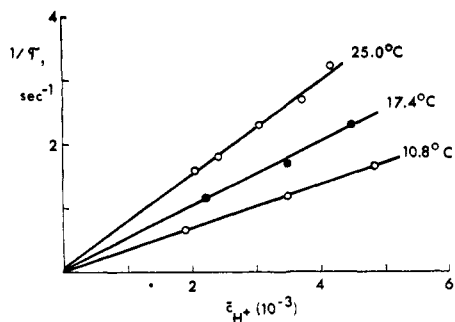


Figure 2. Relaxation rate vs. hydrogen ion concentration at three temperatures for the protonation equilibrium of pseudoisocyanine (cyanine 4) at  $\mu = 0.20$ .

Table II. Kinetic Data on the Protolysis of Pseudoisocyanine (Cyanine 4),  $\mu = 0.20 \mu$  (KNO<sub>3</sub>)

$T$ , °C	pH	$\bar{c}_{H^+}$ <sup>b</sup>	$\tau_{13}$ , msec	$k_{13}$ , M <sup>-1</sup> sec <sup>-1</sup>	$k_{31}$ , sec <sup>-1</sup>	$pK_a$ <sup>a</sup>
25.0	2.50	4.16 (-3)	310	729	7.10 (-2)	4.01
	2.55	3.71 (-3)	369			
	2.63	3.09 (-3)	434			
	2.74	2.40 (-3)	556			
	2.80	2.09 (-3)	625			
17.4	2.47	4.47 (-3)	435	505	3.80 (-2)	4.11
	2.58	3.47 (-3)	595			
	2.78	2.19 (-3)	854			
10.8	2.44	4.79 (-3)	598	350	1.97 (-2)	4.24
	2.58	3.47 (-3)	847			
	2.85	1.86 (-3)	1490			

<sup>a</sup> Determined spectrophotometrically. <sup>b</sup> The figures in parentheses represent powers of ten.

Table III. Rate Constants for Protolysis of Cyanines 2, 3, 4, 5, and 6 at 25.0°,  $\mu = 0.2$

Cyanine	$pK_a$	$k_{13}$ , M <sup>-1</sup> sec <sup>-1</sup>	$k_{31}$ , sec <sup>-1</sup>
2	6.1	$2.2 \times 10^3$	$1.4 \times 10^{-3}$
3	4.6	$1.0 \times 10^3$	$2.4 \times 10^{-2}$
4	4.01	$7.29 \times 10^2$	$7.10 \times 10^{-2}$
5	3.78	$4.2 \times 10^2$	$7.0 \times 10^{-2}$
6	4.74	$1.6 \times 10^3$	$2.9 \times 10^{-2}$

constants which were either determined spectrophotometrically (cyanine 4) under identical conditions of ionic strength and temperature or taken from the literature. The low values for the protonation rate constants in general are noteworthy. For example, for cyanine 4,  $k_{13} = 729 \pm 70 \text{ M}^{-1} \text{ sec}^{-1}$  and  $k_{31} = 7.1 \times 10^{-2} \text{ sec}^{-1}$  at 25°. A clear trend is observed in the benzo-substituted cyanines 2, 3, 4, and 5:  $k_{13}$  increases with increasing  $pK_a$  and decreasing change in  $\pi$ -electron delocalization energy. Ethoxyl substitution (cyanine 6) shows a higher protonation rate constant than that of cyanine 4.

**Proton Transfer.** The kinetics of proton transfer to the various cyanines was studied using a number of "weak" oxygen acids as second acid-base pairs. In all cases the  $pK_a$  of the latter was within  $\pm 2$  units of the  $pK_a$  of the cyanine in order to ensure that finite concentrations of all species taking part in the elementary process were present at equilibrium. At the same time the  $H^+$  concentration was low. For example, the pH values of the solutions containing cyanine

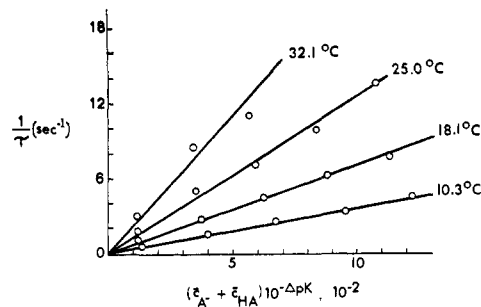
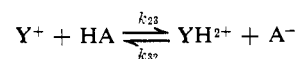


Figure 3. Relaxation rate according to eq 5 at four temperatures for proton transfer between pseudoisocyanine and acetic acid at pH 4.7,  $\mu = 0.2$ .

4 were set at 4.7. At this pH the relaxation time for protolysis is approximately 10 sec as extrapolated from Figure 2. Thus the slow protolysis does not interfere in any significant way with the faster proton transfer at sufficiently low  $H^+$  concentrations. The two equilibria can therefore be observed separately. For the proton transfer path  $2 \leftrightarrow 3$



one has

$$1/\tau_{23} = k_{23}(\bar{c}_{Y^+} + \bar{c}_{HA}) + k_{32}(\bar{c}_{YH^{2+}} + \bar{c}_{A^-}) \quad (3)$$

Since  $\bar{c}_{Y^+}$  and  $\bar{c}_{YH^{2+}}$  are present in indicator concentrations they can be neglected with respect to  $\bar{c}_{HA}$  and  $\bar{c}_{A^-}$ . Therefore eq 3 reduces to

$$1/\tau_{23} = k_{23}(\bar{c}_{HA}) + k_{32}(\bar{c}_{A^-}) \quad (4)$$

For

$$\Delta pK = pK_{HA} - pK_{YH^{2+}} \text{ and } k_{32}/k_{23} = 10^{\Delta pK}$$

substitution yields

$$1/\tau_{23} = k_{32}(\bar{c}_{A^-} + \bar{c}_{HA}) 10^{-\Delta pK} \quad (5)$$

or

$$1/\tau_{23} = k_{23}(\bar{c}_{A^-} 10^{\Delta pK} + \bar{c}_{HA}) \quad (6)$$

Table IV gives details on a number of kinetic runs including relaxation times for the acetic acid-cyanine 4 system at four different temperatures. A plot of eq 5 is shown in Figure 3 for cyanine 4 as a representative example. Straight lines are obtained which pass through the origin. Table V summarizes all proton-transfer rate constants determined in a similar fashion for a number of second acid-base pairs that were coupled with cyanines 2, 3, 4, 5, and 6 at  $\mu = 0.20$ .

Literature values for the  $pK_a$  of deuterioacetic acid in  $D_2O$  at various temperatures were corrected to  $\mu = 0.2$  by the use of activity coefficient of 0.77. The  $pK_a$  of cyanine 4 in  $D_2O$  was determined in this work as a function of temperature at  $\mu = 0.20$  (Table I).

**Activation Energies.** Activation parameters (Table VI) associated with protolysis, proton transfer to acetic acid, and deuteron transfer to deuterioacetic acid have been calculated from Tables II and V for the cyanine 4 system at  $\mu = 0.20$ .

A characteristic feature emerges. The transfer of protons to the carbon from either  $H_3O^+$  or acetic acid proceeds with activation energies of 8.7 and 8.4 kcal/mol

Table IV. Proton Transfer for the Cyanine 4-Acetic Acid System,  $\mu = 0.20$ 

$T, ^\circ\text{C}$	$\text{p}K_a^a$ (HAc)	$\text{p}K_a^a$ (YH <sup>2+</sup> )	$\bar{c}_A, M$	$\bar{c}_{HA},^b M$	pH	$\tau, \text{msec}$	$k_{32}, M^{-1} \text{sec}^{-1}$	$k_{23}, M^{-1} \text{sec}^{-1}$
32.1	4.51	3.91	9.5 (-3)	7.5 (-3)	4.72	333	220	55.3
			2.85 (-2)	2.25 (-2)		120		
			4.74 (-2)	3.76 (-2)		91		
25.0	4.51	4.01	9.5 (-3)	7.5 (-3)	4.72	621	123	38.9
			2.85 (-2)	2.25 (-2)		197		
			4.74 (-2)	3.76 (-2)		140		
			6.70 (-2)	5.30 (-2)		101		
			8.60 (-2)	6.80 (-2)		74		
18.1	4.52	4.11	9.27 (-3)	7.73 (-3)	4.72	961	69.5	27.7
			2.78 (-2)	2.32 (-2)		370		
			4.64 (-2)	3.86 (-2)		220		
			6.54 (-2)	5.46 (-2)		160		
			8.40 (-2)	7.00 (-2)		130		
10.3	4.53	4.24	9.18 (-3)	7.82 (-3)	4.72	1780	36.5	19.1
			2.76 (-2)	2.34 (-2)		671		
			4.59 (-2)	3.91 (-2)		382		
			6.48 (-2)	5.52 (-2)		300		
			8.32 (-2)	7.08 (-2)		220		

<sup>a</sup> H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolyte Solutions," Reinhold, New York, N. Y., 1958. <sup>b</sup> The figures in parentheses represent powers of ten.

Table V. Rate Constants for Proton Transfer,  $\mu = 0.20$ 

Second acid-base pair	$T, ^\circ\text{C}$	$\text{p}K_a$	pH	$k_{23}, M^{-1} \text{sec}^{-1}$	$k_{32}, M^{-1} \text{sec}^{-1}$
Cyanine 2, $\text{p}K_a = 6.19; 25.0^\circ$					
Chloroacetic	25.0	2.62 <sup>b</sup>	5.00	$7.18 \times 10^3$	2.27
Acetic	25.0	4.51 <sup>c</sup>	6.50	$1.1 \times 10^3$	$2.75 \times 10^1$
Phosphoric	25.0	6.73 <sup>d</sup>	6.85	$3.35 \times 10^2$	$1.43 \times 10^3$
Cyanine 3, $\text{p}K_a = 4.60; 25.0^\circ$					
Chloroacetic	25.0	2.62 <sup>b</sup>	4.85	$7.70 \times 10^2$	$1.20 \times 10^1$
Acetic	25.0	4.51 <sup>c</sup>	4.70	$8.85 \times 10^1$	$7.00 \times 10^1$
Cyanine 4, $\text{p}K_a = 4.01; 25.0^\circ$					
$\alpha$ -Aminoacetic	25.0	2.35 <sup>e</sup>	4.47	$3.72 \times 10^2$	7.38
Chloroacetic	25.0	2.62 <sup>b</sup>	4.70	$4.42 \times 10^2$	$1.80 \times 10^1$
Formic	25.0	3.48 <sup>b</sup>	4.70	$8.11 \times 10^1$	$2.39 \times 10^1$
Benzoic	25.0	3.94 <sup>d</sup>	4.70	$1.91 \times 10^2$	$1.62 \times 10^2$
Acetic	10.3 (4.24) <sup>a</sup>	4.53 <sup>c</sup>	4.72	$1.91 \times 10^1$	$3.65 \times 10^1$
	18.1 (4.11) <sup>a</sup>	4.52 <sup>c</sup>	4.72	$2.77 \times 10^1$	$6.95 \times 10^1$
	25.0 (4.01) <sup>a</sup>	4.51 <sup>c</sup>	4.72	$3.89 \times 10^1$	$1.23 \times 10^2$
	32.1 (3.91) <sup>a</sup>	4.51 <sup>c</sup>	4.72	$5.53 \times 10^1$	$2.20 \times 10^2$
Deuterioacetic	10.0 (4.86) <sup>a</sup>	5.03 <sup>f</sup>	4.66	3.10	4.40
	16.1 (4.75) <sup>a</sup>	5.02 <sup>f</sup>	4.66	4.40	8.35
	18.1 (4.71) <sup>a</sup>	5.02 <sup>f</sup>	4.66	4.67	9.52
	25.0 (4.59) <sup>a</sup>	5.01 <sup>f</sup>	4.66	7.00	$1.84 \times 10^1$
	31.9 (4.48) <sup>a</sup>	5.00 <sup>f</sup>	4.66	9.43	$3.12 \times 10^1$
Maleic	25.0	5.57 <sup>d</sup>	4.75	$1.27 \times 10^1$	$4.62 \times 10^2$
Phosphoric	25.0	6.73 <sup>d</sup>	5.57	$1.36 \times 10^1$	$7.15 \times 10^3$
Cyanine 5, $\text{p}K_a = 3.78, 25.0^\circ$					
Chloroacetic	25.0	2.62 <sup>b</sup>	4.68	$9.53 \times 10^2$	$3.14 \times 10^1$
Acetic	25.0	4.51 <sup>c</sup>	4.65	$3.68 \times 10^1$	$1.93 \times 10^2$

<sup>a</sup>  $\text{p}K_a$  of cyanine, determined spectrophotometrically. <sup>b</sup> M. M. Kreevoy and R. Eliason, *J. Phys. Chem.*, **72**, 1313 (1968). <sup>c</sup> H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958. <sup>d</sup> Corrected to  $\mu = 0.2$  using 0.77 for the activity coefficient. <sup>e</sup> G. Kortüm, W. Vogel, and K. Andrussov, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworths, London, 1961. <sup>f</sup> R. Gary, R. G. Bates, and R. A. Robinson, *J. Phys. Chem.*, **69**, 2750 (1965).

Table VI. Arrhenius and Activated Complex Parameters for Cyanine 4,  $\mu = 0.20^a$ 

	$k_{13}$	$k_{31}$	$k_{23}^b$	$k_{32}^b$	$k_{23}^c$	$k_{32}^c$
Log $A$	9.23	8.56	7.74	12.48	7.28	12.50
$E_a$ , kcal/mol	$8.7 \pm 1.4$	$15.0 \pm 1.3$	$8.4 \pm 0.8$	$14.2 \pm 0.8$	$8.8 \pm 0.7$	$15.4 \pm 0.7$
$\Delta S^\ddagger$ , eu	$-18.2 \pm 4.8$	$-21.1 \pm 4.4$	$-25.1 \pm 3.6$	$-3.4 \pm 3.6$	$-27.2 \pm 3.5$	$-3.3 \pm 3.4$
$\Delta H^\ddagger$ , kcal/mol	$8.1 \pm 1.4$	$14.4 \pm 1.3$	$7.8 \pm 0.8$	$13.6 \pm 0.8$	$8.2 \pm 0.7$	$15.4 \pm 0.7$

<sup>a</sup> All standard deviations are based on a 10% standard deviation of the experimental rate constants. The average fit of the numerical  $k$  values to the Arrhenius and transition state expressions is  $\pm 2\%$ . <sup>b</sup> Acetic acid. <sup>c</sup> Deuterioacetic acid.

and with low Arrhenius factors of  $10^{9.23}$  and  $10^{7.74}$  corresponding to reaction entropies of  $-18.2$  and  $-25.1$  eu, respectively. Deuteron transfer from deuterioacetic acid shows a slightly higher activation energy

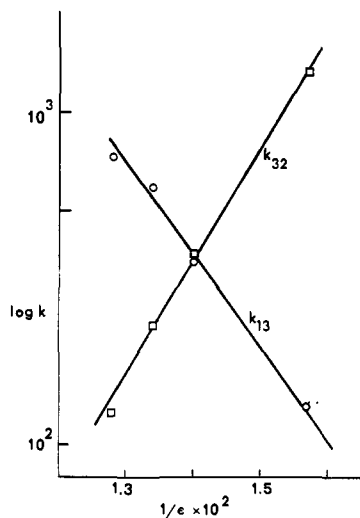


Figure 4. Log  $k$  vs.  $1/\epsilon$  for protonation of cyanine 4 and proton transfer from cyanine 4 to acetate ion in methanol-water solvents at 25° and  $\mu = 0.20$ .

of 8.8 kcal/mol and a slightly lower Arrhenius factor of  $10^{7.28}$  ( $\Delta S^\ddagger = -27.2$  eu). The activation energy of the reverse step, the transfer of a proton from the carbon to the oxygen of  $H_2O$  as acceptor, is 15.0 kcal/mol accompanied by a similarly low Arrhenius factor of  $10^{8.56}$  ( $\Delta S^\ddagger = -21.1$  eu). Proton and deuteron transfer from carbon to the acetate ion has activation energies of 14.2 and 15.4 kcal/mol with activation entropies of  $-3.4$  and  $-3.3$  eu corresponding to Arrhenius factors of  $10^{12.48}$  and  $10^{12.50}$ , respectively.

**Solvent Isotope Effect.** The solvent isotope effect for the forward and reverse transfer processes for the cyanine 4–acetic acid system can be calculated at three temperatures from the data given in Table V. For example, at 25°,  $k^{H_{32}}/k^{D_{32}} = 6.68$  and  $k^{H_{23}}/k^{D_{23}} = 5.56$ . Both isotope effects increase with decreasing temperature (Table VII), with the exception of the

Table VII. Deuterium Solvent Isotope Effect as a Function of Temperature for Proton Transfer in the Cyanine 4–Acetic Acid System,  $\mu = 0.20$

$T, ^\circ C$	$k^{H_{23}}/k^{D_{23}}$	$k^{H_{32}}/k^{D_{32}}$	$\frac{k^{H_{23}}/k^{D_{23}}}{k^{H_{32}}/k^{D_{32}}}$
10.3	6.11 <sup>a</sup>	8.10 <sup>a</sup>	0.755
18.1	5.93	7.30	0.811
25.0	5.56	6.68	0.832
32.1	5.88 <sup>a</sup>	6.65 <sup>a</sup>	0.885

<sup>a</sup>  $k^D$  values are extrapolated at this temperature.

point for  $k^{H_{23}}/k^{D_{23}}$  at 32.1° which may be due to experimental error. The difference in activation energies is  $\Delta E_{23} = E_H - E_D = -0.4$  kcal/mol and  $\Delta E_{32} = -1.2$  kcal/mol.

**Kinetic Salt Effect.** The effect of ionic strength on proton transfer between cyanine 4 and acetic acid has been measured for  $\mu = 0.2, 0.65,$  and  $1.0$ . To calculate  $k_{32}$  and  $k_{23}$  from eq 5 and 6, respectively, it is necessary to know the  $\Delta pK$  as a function of  $\mu$ . Feldman, *et al.*,<sup>8</sup> determined the  $pK_a$  of cyanine 4 as 4.40 (at 525 nm) for a total cyanine concentration of  $3 \times 10^{-5}$  M in 1.0 M KCl at 24°. In this work we use a pro-

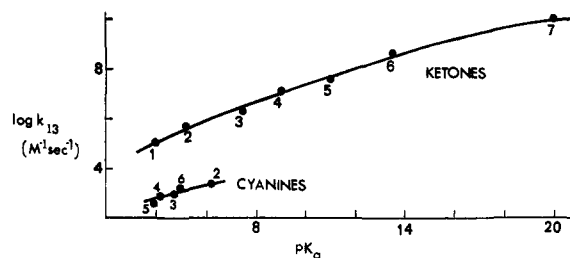


Figure 5. Log  $k_{13}$  ( $M^{-1} \text{sec}^{-1}$ ) vs.  $pK_a$  for cyanines given in Figure 1 and the text, and for ketones:<sup>17</sup> (1) barbituric acid, (2) Meldrum's acid, (3) diacetylacetone, (4) acetylacetone, (5) ethylacetylacetone, (6) diethylmalonic acid, and (7) acetone.

cedure in conjunction with the kinetic data that starts with an arbitrary value for  $\Delta pK_a$  which is then refined by iterative least-squares calculations of eq 5 until the relation  $k_{32}/k_{23} = 10^{\Delta pK}$  is satisfied. In this procedure it had to be assumed that the back reaction,  $k_{23}$ , is practically independent of ionic strength. The values for  $k_{32}$  were calculated to be 125, 82, and  $50 M^{-1} \text{sec}^{-1}$ , respectively, and the final value of the  $pK_a$  of cyanine 4 is 4.40 at  $\mu = 1.0$  ( $KNO_3$ ) in agreement with the results of Feldman, *et al.* Since  $k_{32}$  decreases with ionic strength it can be concluded that the reaction occurs between unlike charges (acetate ion and the cyanine acid,  $YH^{2+}$ ) as expected. There exists no adequate theoretical expression for the effect of the large ionic strengths used in this study upon the rate constants.

**Effect of Dielectric Constant in the Methanol–Water System.** The rates of protolysis and proton transfer (acetic acid system) involving cyanine 4 were measured in 8.1, 16.3, and 33.3% methanol–water mixtures where  $\mu$  was constant at 0.2 with  $KNO_3$  as the inert electrolyte. The glass electrode was standardized using buffer mixtures described by Bates, *et al.*,<sup>14</sup> in solvents of exactly the same composition<sup>15</sup> as that in which the kinetic measurements were made.<sup>16</sup> A spectrophotometric determination of the  $pK_a$  of pseudoisocyanine in the above solvent mixtures leads to the values 3.86, 3.45, and 3.10 (25°), respectively. The kinetic results are summarized in Table VIII. The activity coefficients employed for all conversions from pH to  $\bar{c}_H^-$  refer to 0.2 m HCl in methanol–water mixtures at 25°. The reaction mechanism of protolysis and proton transfer was assumed to be identical with that in pure water. A marked decrease of  $k_{13}$  and  $k_{23}$  with decreasing  $\epsilon$  is found. Plots of  $\log k_{13}$  and  $\log k_{32}$  vs. the reciprocal dielectric constant are linear with a negative and positive slope, respectively (Figure 4).

## Discussion

In this work the “low” rate constants for proton transfer from  $H_3O^+$  to the methine carbon in several 2,2'-cyanines are found to be five to seven orders of magnitude below diffusion controlled. In fact they are two orders of magnitude smaller than those for the protonation of certain ketones of similar  $pK_a$  (Figure 5).<sup>17</sup> A comparable protonation rate constant of 7.5

(14) R. G. Bates, M. Paabo, and R. A. Robinson, *J. Phys. Chem.*, **67**, 1833 (1963).

(15) A. L. Bacarella, E. Grunwald, H. P. Marshall, and E. Lee Purlee, *ibid.*, **62**, 856 (1958).

(16) R. P. Jenson, E. M. Eyring, and W. M. Walsh, *ibid.*, **70**, 2264 (1966).

(17) J. Stuehr, *J. Amer. Chem. Soc.*, **89**, 2826 (1967).

Table VIII. Protolysis and Proton Transfer in Methanol-Water as Solvent for Cyanine 4 at 25.0°,  $\mu = 0.20$ 

Wt. % methanol	$\epsilon^{13}$	$\gamma^{13}$	$pK_a^a$ , cyanine 4	$pK_a$ , acetic acid	$k_{13}$ , $M^{-1} \text{sec}^{-1}$	$k_{31}$ , $\text{sec}^{-1}$	$k_{23}$ , $M^{-1} \text{sec}^{-1}$	$k_{32}$ , $M^{-1} \text{sec}^{-1}$
0.0	78.3	0.77	4.01	4.51	729	0.07	38.9	123
8.1	75.0	0.75	3.86	4.63	596	0.09	37.2	224
16.3	71.5	0.73	3.44	4.76	351	0.30	16.9	366
33.3	63.7	0.70	3.06	5.00	131	0.41	13.0	1300

<sup>a</sup> Determined spectrophotometrically in this work.

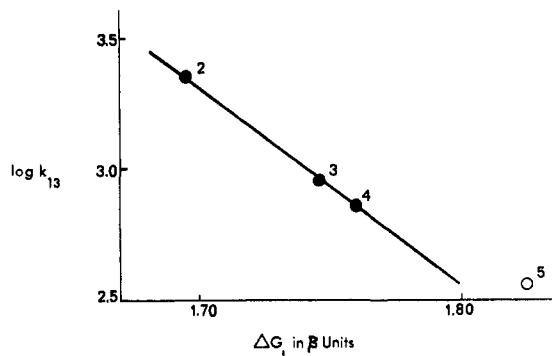


Figure 6.  $\log k_{13}$  vs.  $\Delta G_{100}$  for various cyanines<sup>2</sup> given in Figure 1 at 25° and  $\mu = 0.20$ . For the deviation of cyanine 5 see text.

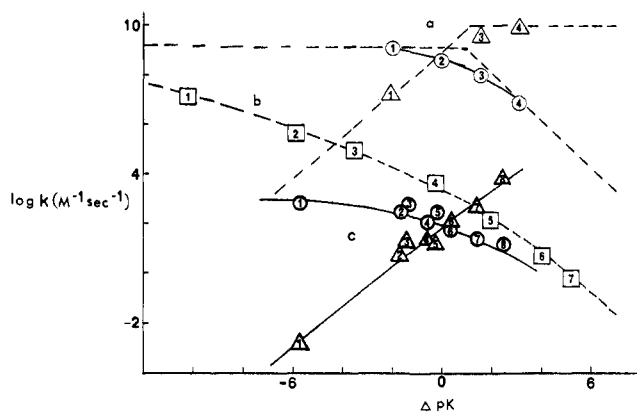


Figure 7. Brønsted plots for proton transfer. (a) Imidazole:<sup>2a</sup> second acid-base pairs are (1) phenol, (2)  $\text{HP}_2\text{O}_7^{3-}$ , (3) *p*-nitrophenol, (4) acetic acid; circles,  $k_{23}$ ; triangles,  $k_{32}$ . (b) Acetylacetone:<sup>3</sup> (1)  $\text{H}_3\text{O}^+$ , (2) chloroacetic acid, (3) dimedone, (4) *O*-chlorophenol, (5) trimethylphenol, (6) mannose, (7)  $\text{H}_2\text{O}$ ; squares,  $k_{23}$ . (c) Pseudoisocyanine (this work), 25° and  $\mu = 0.20$ : (1)  $\text{H}_3\text{O}^+$ , (2) glycine, (3) chloroacetic acid, (4) formic acid, (5) benzoic acid, (6) acetic acid, (7) maleic acid, (8)  $\text{H}_2\text{PO}_4^-$ ; circles,  $k_{23}$ ; triangles,  $k_{32}$ .

$\times 10^2 M^{-1} \text{sec}^{-1}$  is known for  $\text{CH}_3\text{COCH}_2\text{COCF}_3^{18}$  ( $pK_a = 4.7$ ). Lower rate constants for protonation of carbon have been measured for  $\text{CH}_3\text{NO}_2$  ( $pK_a = 10.2$ ) and  $\text{C}_2\text{H}_5\text{NO}_2$  ( $pK_a = 8.60$ ) whose values are  $6.8 \times 10^2$  and  $1.5 \times 10^2 M^{-1} \text{sec}^{-1}$ , respectively.<sup>18</sup> On the other hand, one group of nonaromatic carbon acids, the cyanocarbons, has been recently shown to exhibit protonation behavior that is virtually diffusion controlled.<sup>19</sup>

Figure 5 shows that the *slope* of the curve of  $\log k_{13}$  vs.  $pK_a$  is lower for the 2,2'-cyanines than for the keto

(18) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 161, and references cited therein.

(19) E. A. Walters and F. A. Long, *J. Amer. Chem. Soc.*, **91**, 3733 (1969); F. Hibbert, F. A. Long, and E. A. Walters, *ibid.*, **93**, 2829 (1971); F. Hibbert and F. A. Long, *ibid.*, **93**, 2836 (1971); in press. (We thank the authors for a preprint of their paper.)

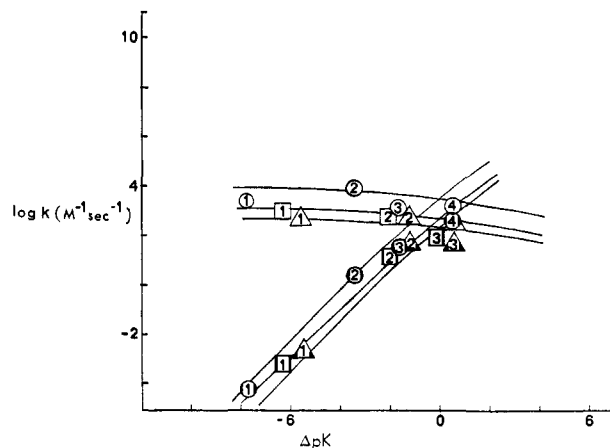


Figure 8. Brønsted plots for proton transfer, 25° and  $\mu = 0.20$ . Cyanine 2 (circles): (1)  $\text{H}_3\text{O}^+$ , (2) chloroacetic acid, (3) acetic acid, (4) phosphoric acid. Cyanine 3 (squares): (1)  $\text{H}_3\text{O}^+$ , (2) chloroacetic acid, (3) acetic acid. Cyanine 5 (triangles): (1)  $\text{H}_3\text{O}^+$ , (2) chloroacetic acid, (3) acetic acid.

curve. This behavior indicates that any extrapolated diffusion controlled limit would be attained only at very high  $pK_a$  values ( $pK_a \gg 20$ ). Attainment of a limiting  $\log k_{13}$  value *below* the diffusion controlled limit cannot be ruled out from our data. Such a lower limit would be expected if an equilibrium preceding protonation exists.

In the particular case of cyanines 2, 3, and 4 whose plot of  $pK_a$  vs.  $\Delta G_{100}$  is linear,<sup>2</sup> a linear relationship is obtained in their  $\log k_{13}$  vs.  $pK_a$  plot as well (Figure 5), whose slope is 0.28. Thus a graph of  $\log k_{13}$  vs.  $\Delta G_{100}$  shows a straight line (Figure 6) in an excellent approximation. It should be stressed that cyanine 5 generally shows an appreciable deviation in any  $\Delta G_{100}$  plot which is due most probably to strong steric hindrance to coplanarity<sup>2</sup> in its conjugate base. On the basis of the present experimental scatter we consider the quantitative significance of the linear behavior in *this*  $pK_a$  range well established although only three points are available. Thus the linear free energy relationship between equilibrium properties such as  $pK_a$  and  $\Delta G_{100}$  also manifests itself in the kinetics of protonation in *this*  $pK_a$  region.

The Brønsted relation of  $\log k_{32}$  vs.  $\Delta pK_a$  for cyanine 4 shows a curve that lies below that of acetylacetone (Figure 7). Furthermore, the Brønsted coefficient  $\alpha$  is about 0.20 at  $\Delta pK = 0$  irrespective of whether the  $\text{H}_3\text{O}^+$  data point at  $\Delta pK_a = -5.78$  is included or not, and the graphically extrapolated limiting value for  $k_{23}$  is about  $8 \times 10^2 M^{-1} \text{sec}^{-1}$  for cyanine 4. A comparison of the Brønsted plots for cyanines 2, 3, and 5 (Figure 8) shows that limiting behavior (zero slope) seems to have been attained as well although the data are not quite as extensive as those for cyanine 4. The *limiting transfer* rate constants increase as the  $pK_a$

of the cyanine increases. Therefore it follows that the limiting rate of proton transfer to the carbon is a function of the change in  $\pi$ -electron delocalization energy similar to the behavior of the protonation rate constants  $k_{13}$ .

It should be mentioned that application of statistical factors has not been made owing to their relative ambiguity.<sup>18</sup> Rate constant ratios are consistent with the respective thermodynamic equilibrium constant in all cases.

Activation parameters have been measured for cyanine 4. An activation energy of 8.7 kcal/mol for proton transfer from  $\text{H}_3\text{O}^+$  to the carbon of cyanine 4 in water as the solvent leads to a low Arrhenius factor of  $10^{9.23}$  corresponding to  $\Delta S^\ddagger = -18.2$  eu. This highly negative activation entropy which seems to be typical for some other protonation reactions of carbon may be rationalized partially on the basis of a relatively short reaction distance between the hydronium ion and the carbon atom, if one considers the traditional relationship<sup>20</sup> between  $\Delta S^\ddagger$  and the dielectric constant ionic strength (eq 77 or ref 20). For this reaction  $\log k_{13}$  vs.  $1/\epsilon$  (methanol-water) shows a straight line of negative slope (Figure 4) indicating that the reaction occurs between ions of like (positive) sign.<sup>20</sup> The interionic distance calculated from the latter slope is of the same low order of magnitude as that calculated from  $\Delta S^\ddagger$  (for pure water as the solvent). It should be stressed that the use of the macroscopic dielectric constant is not strictly valid especially for the seemingly very short reaction distances encountered in this work. For this reason the numerical values of the calculated interionic distances have no quantitative significance and they are not cited. However, these *order of magnitude* calculations are not inconsistent with Kreevoy and Williams<sup>21</sup> conclusions that the proton may be transferred directly from  $\text{H}_3\text{O}^+$  to the non-hydrogen-bonded carbon without any intervening water molecules in the hydrolysis of ethyl vinyl ether in DMSO- $\text{H}_2\text{O}$  solvents where proton transfer is rate determining. Furthermore, Albery<sup>22</sup> contends that transfers to non-hydrogen-bonded substrates are likely to proceed directly *via* the  $\text{H}_3\text{O}^+$  unit.

The reverse step, proton transfer from the carbon to the water molecule, is accompanied by an activation entropy of  $-21.1$  eu and an activation energy of 15.0 kcal/mol. The Brønsted coefficient  $\beta$  is close to unity which is usually taken to indicate that proton transfer in the transition state is practically complete. Here the rate constant decreases with increasing dielectric constant (Table VIII) which is in qualitative but not quantitative agreement with predictions for reaction between an ion and a neutral molecule.

Proton transfer from the acetic acid molecule to the methine carbon of cyanine 4 shows an equally low Arrhenius factor of  $10^{7.74}$  and  $E_a = 8.4$  kcal/mol. Reaction occurs formally between a positive ion and a neutral molecule. However, the prediction for reaction between ions and dipoles<sup>20</sup> is not borne out here; the

proton-transfer rate constant increases substantially with increasing dielectric constant (Table VIII).

Reverse proton transfer from the formally doubly positive carbon acid molecule to the acetate ion as a catalyst has an Arrhenius factor of  $10^{12.5}$  and an activation energy of 14.2 kcal/mol. From the slope of the  $\log k_{32}$  vs.  $1/\epsilon$  plot (Figure 4) one obtains a reaction distance of a similarly low order of magnitude as for the protonation reaction ( $k_{13}$ ). The "kinetic"  $\text{p}K_a$  values calculated for cyanine 4 in  $\text{CH}_3\text{OH}-\text{H}_2\text{O}$  mixtures are found to be somewhat lower than the  $\text{p}K_a$  values determined spectrophotometrically in this work (Table VIII). This (mild) discrepancy found for increasing  $\text{CH}_3\text{OH}$  composition may point to anomalies occurring in methanol-water mixtures upon a change in solvent composition.

The value for the overall kinetic isotope effect at 25° found for the 32 step (= 6.7) involving breakage of a CH bond would seem reasonable in light of attempted interpretations that are based on the difference in zero point energies for the CH and CD stretching vibrations.<sup>18</sup> However, since the pure solvents  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  were used and since any transition state should be strongly polar, the medium effect should make an important contribution in addition to the primary kinetic isotope effect in both directions neither of which are diffusion controlled. The exact value of the primary kinetic isotope effect is not known barring any calculations that involve conjectures as to the structure of a transition state. Mixed solvent measurements would be helpful. A possible secondary isotope effect due to exchange of the methine hydrogen with  $\text{D}_2\text{O}$  should be quite small ( $\approx 1$ ). The overall kinetic isotope effect measured in the acetic acid system may be close to the maximum for the cyanine 4 system since  $\Delta \text{p}K \approx 0$ . The effect in both directions decreases with increasing temperature as expected from a simple Arrhenius type expression. Their ratios are close to unity as required by the overall equilibrium constant.

The kinetic salt effect is consistent regarding charge type with the assignment of relaxation times. Thus the dependence of the rate constants upon ionic strength and changes in dielectric constant generally follow qualitative predictions based on the *charge* of the molecule, whereas the absolute magnitude of respective rate constants should be governed by the *polarity* of the accepting carbon atom. Calculations are in progress to show directly to which extent the electron density on the methine carbon is affected by delocalization and, in turn, how its polarity correlates with the magnitude and variation of the protonation and deprotonation rate constants. It is most likely that the lower the polarity of the methine carbon due to enhanced delocalization the lower is the rate of protonation. Further work is in progress to determine the  $\text{p}K_a$  values and proton transfer rates for cyanines in their electronically excited singlet states where the methine carbon polarity has been significantly altered within the same molecule.

**Acknowledgment.** F. W. S. thanks Dr. M. M. Kreevoy for an interesting discussion and Dr. S. K. Podder for his early interest in this work. Thanks are expressed to Dr. G. Schwarz, University of Basel, Switzerland, for the hospitality extended to F. W. S. during which time part of this manuscript was written.

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