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Uncommon Interactions of Aliphatic Dicarboxylic Acids with Cyclodextrins

ORSOLYA CSERNÁK[1], ÁGNES BUVÁRI-BARCZA[1,*], JÁNOS SAMU[2] and LAJOS BARCZA[1]

[1]*Department of Inorganic and Analytical Chemistry, L. Eötvös University;* [2]*Department of Organic Chemistry, [L. Eötvös University] H-1117 Budapest, Pázmány Péter sétány 1/A, Hungary*

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Abstract

A relatively high and unexpected increase of inclusion complex stabilities could be detected in some half dissociated dicarboxylic acids (HA^- ions) with *intramolecular* H-bonding. The *intermolecular* hydrogen bonds between the protruding functional groups of the guest and the hydroxy groups of the host are known to enhance the stability of the cyclodextrin (CD) inclusion complexes. The enhanced inclusion of HA^- species is promoted, not by the intermolecular but by the intramolecular H-bond indirectly, resulting in a compact shape of the guest with more favourable space filling.

Introduction

The hydrophobic (though relatively polar) inner cavity of cyclodextrins (CDs) is of main importance in the formation of their inclusion complexes [1]. The van der Waals interactions in the cavity prefer the inclusion of aromatic type guest molecules, but the possibility of hydrogen bond formation between the CDs' outer hydroxy groups, and the guest molecule can significantly enhance the stability of the supramolecule.

The study of the effect of hydrogen bonding in stabilization of inclusion complexes has been one of our special fields for a long time [2], and the rather unique interaction between the benzoic acid and β-CD could be interpreted as hydrogen bonding [3]. The difference among the formation constants of β-CD complexes with acetic acid and some aromatic carboxylic acids [2] is an evidence of the higher stability of the complexes with molecules with aromatic substituents.

A lot of data are also known about the complexation of aliphatic acids. For instance, the complex formation of aliphatic organic acids and CDs was studied by freezing point depression method [4] or by potentiometry, solubility and competitive spectrophotometry [5]. The higher normal chain monocarboxylic acids (C8–16) form inclusion complexes of 2:1 or 3:1 stoichiometries (CD:acid) over the general 1:1 composition [6, 7].

The stabilities of the inclusion complexes with the undissociated acid and its conjugated anion can differ significantly, since the carboxylate ion is always more hydrated; therefore, its inclusion is less favoured. The organic acids are investigated very often at higher pH (pH >7); therefore, the measured constants are mixed (including those for the undissociated acid and for the anion or valid only for the anion) [8]. Most of the results measured with "organic acids" by microcalorimetry are valid only for their deprotonated anion [9–12].

Concerning the effect of the H-bond, some very interesting findings occur, as some HA^- type (half dissociated) species of aliphatic dicarboxylic acids form more stable inclusion complexes with α-CD than the undissociated acid itself [13]. The phenomena have been neither investigated nor explained in detail.

To gain deeper insight into the special effect of H-bonding on inclusion complex formation, the behaviour of the following acids in presence of β-CD have been investigated: aliphatic α,ω-dicarboxylic acids from oxalic acid up to adipic acid, diethylmalonic acid, maleic acid and fumaric acid.

The connection between protonation (dissociation) and complex formation equilibria is represented in Scheme 1.

$$\begin{array}{ccccc} \mathbf{H_2A} & \leftrightarrow & \mathbf{HA^-} & \leftrightarrow & \mathbf{A^{2-}} \\ \updownarrow & & \updownarrow & & \updownarrow \\ \mathbf{D{\cdot}H_2A} & \leftrightarrow & \mathbf{D{\cdot}HA^-} & \leftrightarrow & \mathbf{D{\cdot}A^{2-}} \end{array}$$

Scheme 1. Connections among the acidic dissociation and inclusion complex formation equilibria in aliphatic dicarboxylic acid–β-CD systems.

* Author for correspondence. E-mail: barcza@para.chem.elte.hu

The formation (dissociation or stability) constants were determined by pH–potentiometry combined with competitive spectrophotometric measurements.

Methods and materials

Diethyl malonic (diethyl propanedioic) acid was prepared from malonic acid by the common procedure [14]. The β-CD (CYCLOLAB Ltd, Budapest, Hungary) and the glutaric acid were recrystallized from hot water. The reagent-grade phenolphtalein was recrystallized from an ethanol–water mixture. All the other materials were of analytical grade and used without further purification. Carbonate free NaOH was prepared by the Sörensen method. The solutions were made with doubly distilled water.

Potentiometric method

The pH–potentiometric titration is the most frequently applied method of the coordination chemistry for the studies of complex equilibria when the interactions are connected with the change of the hydrogen ion concentration [15], and it can be similarly used to follow the interactions of CDs in many cases too.

When CD is added to the solution of organic acids, the protonation equilibria are shifted as a consequence of inclusion complex formation (see Scheme 1). The interactions can be characterized by the general relationship:

$$p\mathrm{H}^+ + q\mathrm{A}^{a-} + r\mathrm{D} \Leftrightarrow \mathrm{H}_p\mathrm{A}_q\mathrm{D}_r^{(qa-p)-} \qquad (1)$$

where H^+ is the hydrogen (hydroxonium) ion, A^{a-} is the carboxylate ion and D is β-CD. The general formation constant can be defined as:

$$\beta_{pqr} = \frac{[H_pA_qD_r^{(qa-p)-}]}{[H^+]^p[A^{a-}][D]^r} \qquad (2)$$

We found in the present work that $q = r = 1$, i.e. 1:1 acid:CD inclusion complexes are formed. The numerical value of a is 2 in the case of dicarboxylate anions.

The individual formation constants for the complexes of the various protonated dicarboxylate anions can be derived as:

$$\mathrm{D} + \mathrm{A}^{2-} \Leftrightarrow \mathrm{D}\cdot\mathrm{A}^{2-} \quad K_{011} = \frac{[\mathrm{D}\cdot\mathrm{A}^{2-}]}{[\mathrm{D}][\mathrm{A}^{2-}]} (\equiv \beta_{011}) \quad (3)$$

$$\mathrm{D} + \mathrm{HA}^{-} \Leftrightarrow \mathrm{D}\cdot\mathrm{HA}^{-} \quad K_{111} = \frac{[\mathrm{D}\cdot\mathrm{HA}^{-}]}{[\mathrm{D}][\mathrm{HA}^{-}]} = \frac{\beta_{111}}{\beta_{110}} \quad (4)$$

$$\mathrm{D} + \mathrm{H_2A} \Leftrightarrow \mathrm{D}\cdot\mathrm{H_2A} \quad K_{211} = \frac{[\mathrm{D}\cdot\mathrm{H_2A}]}{[\mathrm{D}][\mathrm{H_2A}]} = \frac{\beta_{211}}{\beta_{210}} \quad (5)$$

The total (known) concentrations are:

$$c_\mathrm{H} = 2[\mathrm{H_2A}] + [\mathrm{HA}^-] + 2[\mathrm{D}\cdot\mathrm{H_2A}] + [\mathrm{D}\cdot\mathrm{HA}^-] + [\mathrm{H}^+] \qquad (6)$$

$$c_\mathrm{D} = [\mathrm{D}\cdot\mathrm{H_2A}] + [\mathrm{D}\cdot\mathrm{HA}^-] + [\mathrm{D}\cdot\mathrm{A}^{2-}] + [\mathrm{D}] \quad (7)$$

$$c_\mathrm{A} = [\mathrm{H_2A}] + [\mathrm{HA}^-] + [\mathrm{A}^{2-}] + [\mathrm{D}\cdot\mathrm{H_2A}] + [\mathrm{D}\cdot\mathrm{HA}^-] + [\mathrm{D}\cdot\mathrm{A}^{2-}], \qquad (8)$$

which can be expressed using the values of formation constants (β), e.g.:

$$c_\mathrm{H} = 2\beta_{210}[\mathrm{H}^+]^2[\mathrm{A}^{2-}] + \beta_{110}[\mathrm{H}^+][\mathrm{A}^{2-}] + 2\beta_{211}[\mathrm{D}][\mathrm{H}^+]^2[\mathrm{A}^{2-}] + \beta_{111}[\mathrm{D}][\mathrm{H}^+][\mathrm{A}^{2-}] + [\mathrm{H}^+] \qquad (9)$$

Adding known amounts of an alkali to the solution (titrating with NaOH), the total concentration of acid (c_H) decreases and the pH changes. Knowing the total concentrations and measuring the equilibrium concentration of hydrogen ion, the values of stability constants can be calculated using Equations (9–7) by an iterative computer program (with different sets of equilibrium constants), which searches for the best fit between the experimental and calculated values.

Aliquots of 5×10^{-3}–2×10^{-2} M solutions of dicarboxylic acids were titrated with 0.2 M carbonate free NaOH solution under stirring with nitrogen in the absence and in the presence of 5×10^{-3}, 10^{-2} and 1.4×10^{-2} M β-CD, respectively. The ionic strength was 0.2 M (NaCl), and the temperature was kept at 25 ± 0.1 °C.

Radelkis OP 208/1 pH-meter fitted with a Radelkis OP 0808P combined glass electrode and a Schott-Geräte T80/20 automatic burette was used to obtain potentiometric measurements. This system was calibrated using two different buffers (pH = 4.008 and 6.865) and checked using a third buffer (pH = 9.180).

Remark: as found experimentally, the method can be applied only when the CD complexes of the conjugated acid–base pairs are of different stabilities. This finding can also be proved theoretically, as follows.

The dissociation constants of an uncomplexed and a complexed monovalent organic acid can be characterized as:

$$K_{\mathrm{d(HA)}} = \frac{[\mathrm{H}^+][\mathrm{A}^-]}{[\mathrm{HA}]}, \text{(a) and } K_{\mathrm{d(D\cdot HA)}} = \frac{[\mathrm{H}^+][\mathrm{D}\cdot\mathrm{A}^-]}{[\mathrm{D}\cdot\mathrm{HA}]}, \text{(b)} \qquad (10)$$

(where d in the indices means dissociation), while the formation constants of the appropriate CD complexes are defined as:

$$K_{\mathrm{D\cdot A^-}} = \frac{[\mathrm{D}\cdot\mathrm{A}^-]}{[\mathrm{D}][\mathrm{A}^-]} \quad \text{and} \quad K_{\mathrm{D\cdot HA}} = \frac{[\mathrm{D}\cdot\mathrm{HA}]}{[\mathrm{D}][\mathrm{HA}]}. \quad (11)$$

Expressing $[H^+]$ from Equation (10a) and substituting this into Equation (10b):

$$[H^+] = \frac{K_{d(HA)}[HA]}{[A^-]} \rightarrow K_{d(D\cdot HA)} = \frac{K_{d(HA)}[HA][D\cdot A^-]}{[A^-][D\cdot HA]}. \quad (12)$$

Since the value is unchanged if both the numerator and the denominator is multiplied with [D]:

$$K_{d(D\cdot HA)} = \frac{K_{d(HA)}[HA][D\cdot A^-][D]}{[A^-][D\cdot HA][D]}, \quad (13)$$

after rearranging, the outcome is:

$$K_{d(D\cdot HA)} = K_{d(HA)} \frac{[D\cdot A^-]}{[A^-][D]} \cdot \frac{[HA][D]}{[D\cdot HA]} = K_{d(HA)} \frac{K_{D\cdot A^-}}{K_{D\cdot HA}} \quad (14)$$

If the assumed stability constants of species $D\cdot A^-$ and D·HA are equal, the acidic dissociation constants of complexed and free acids are also equal. It follows that no change in $[H^+]$ is caused by the addition of CD.

An example of the potentiometric titration sets is demonstrated in Figure 1.

Spectrophotometric methods

As shown above in Scheme 1, the equilibria of dissociation and complex formation are strongly coupled; therefore, the potentiometric results are highly recommended to be coupled with other methods. Spectrophotometry was chosen to determine the stability constant of protonated acid with CD in acidic solution and/or that of the dianion in alkaline solution. These methods are based on the competing reactions of two guests (an acid–base indicator and the acid or anion studied) with the CD.

At a given and constant pH, the selected dye has to change its absorption as a consequence of the complex formation. For example, one of the best known acid-base indicators, phenolphthalein (more exactly, its twice deprotonated anion, Ph) is purple in colour at pH = 10.5, but the solution is decolourized by an excess of CD (because the Ph·D complex is colourless [16]). This equilibrium is disturbed by the competing guest (A^{2-}), but the equilibrium concentration of Ph (at $\lambda_{max} = 550$ nm) can be directly measured in these solutions. Knowing the total concentrations and [Ph], the constants can be computed.

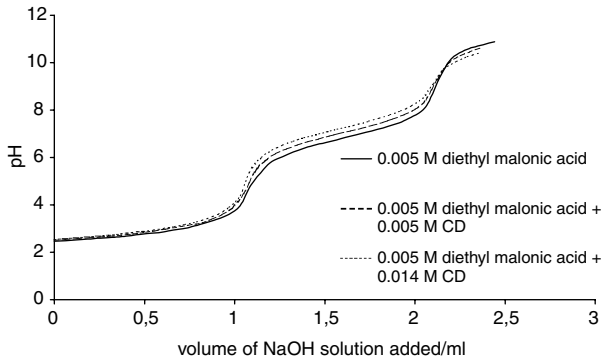

Figure 1. Titration curves of diethyl malonic acid.

Phenolphthalein was used in 3×10^{-5} M concentration (freshly prepared), and the pH was adjusted with 2×10^{-2} M sodium carbonate to pH = 10.5. The CD concentrations varied from zero to 2.5×10^{-4} M (in 12 steps) and those of carboxylate salts from 3.5×10^{-3} to 10^{-1} M (but were constant within a series). The absorbances were measured at $\lambda = 550$ nm. (Further details of the competing method are discussed in an earlier paper [17].)

At pH = 1.0, the azo-type acid–base indicator methyl orange (M) was utilized, existing in acidic solution as a red-coloured protonated species. The intensity of the red colour ($\lambda_{max} = 506$ nm) is significantly decreased in the presence of CD, since the red-coloured azonium–quinoidal form (which is stable in aqueous solution) is transformed during the inclusion to a colourless ammonium-type species [18]. This species has an absorption maximum at 319 nm, and a significant (and proportional) increase in absorbance can be observed upon addition of CD. Using both wavelengths, the (apparent) molar absorptivities (ε_M) of the free indicator can be measured in absence of β-CD, while the changes upon addition of CD can be described in terms of the complex formation. The formation constant of $CD\cdot M$ inclusion complex is defined as:

$$D + M \Leftrightarrow D\cdot M \qquad \beta_{0011} = \frac{[D\cdot M]}{[D][M]} \quad (15)$$

where the fourth figure in the index means the number of indicator molecules in the complex. The absorbance measured can be expressed as:

$$A = \varepsilon_M[M] + \varepsilon_{D\cdot M}[D\cdot M] = \varepsilon_M[M] + \varepsilon_{D\cdot M}\beta_{0011}[D][M] \quad (16)$$

where $\varepsilon_{D\cdot M}$ is the molar absorptivity of the complex at the given wavelength.

The connections of the total concentrations:

$$c_M = [M] + [D\cdot M] = [M] + \beta_{0011}[D][M] \quad (17)$$

and

$$c_D = [D] + [D\cdot M] = [D] + \beta_{0011}[D][M] \quad (18)$$

can be simplified by the assumption that $[D] \approx c_D$, since the CD is present in a relatively large excess.

Measuring the absorbances at different concentrations of CD, both $\varepsilon_{D\cdot M}$ and β_{0011} can be calculated. (The experimental data of two wavelengths were evaluated together.)

In the presence of another potential guest molecule, the absorbance at $\lambda = 506$ nm is decreased less and the increase at $\lambda = 319$ nm is also smaller. The total CD concentration in this case:

$$c_D = [D] + [D \cdot M] + [D \cdot H_2A] = [D] + \beta_{0011}[D][M] + K_{2110}[H_2A][D] \quad (19)$$

The assumption that $[H_2A] \approx c_{acid}$ can be accepted, since the second guest molecule must be used in relatively high concentration (because of the low stability constant), and the dissociation of the weak acids is negligible at pH 1 (except oxalic acid); therefore,

$$c_D = [D] + \beta_{0011}[D][M] + K_{2110} \cdot c_{acid}[D] \quad (20)$$

Methyl orange (2×10^{-5} M) in 0.1 M HCl was used at two different wavelengths ($\lambda = 319$ and 506 nm). The solutions contained 0–6.5×10^{-3} M β-CD and 3.5×10^{-3}–10^{-1} M dicarboxylic acid.

Camspec M330 and Spectromom 195D spectrophotometers were used with 10 mm cells. The temperature was kept constant at 25 ± 1 °C.

Results and discussion

The equilibrium constants for the β-CD complexes obtained are summarized in Table 1.

The measured dissociation constants of the dicarboxylic acids are shown in the first and second columns of Table 1, and they correspond fairly with data in the literature [19].

The effect of the intramolecular H-bond in the HA^- species is well demonstrated with the K_{d1}/K_{d2} ratios, especially with those of the maleic acid–fumaric acid *cis–trans* isomer pair. Since the C=C bond is rigid, the two carboxylic groups are far from each other in the *trans* isomer (fumaric acid) and they cannot interact; therefore, the two steps of acidic dissociation are nearly independent ($K_{d1}/K_{d2} \approx 25$). In contrast to this species, the two carboxylic groups are forced together in the *cis* form (maleic acid), and the formation of the intramolecular hydrogen bond is highly preferred. Because of the electron withdrawing effect of the accumulated oxygens in this structure, one of the carboxylic groups is compelled to dissociate, while the second one remains in the H-bond. The consequence is the high difference between the two dissociation constants: $K_{d1}/K_{d2} \approx 10^4$.

The electron withdrawing effect of the accumulated oxygens (originated by the intramolecular H-bond) is clearly manifested in the great K_{d1} constant of oxalic acid. Because of the considerable dissociation, the undissociated oxalic acid is a minor component in aqueous solutions, and this is the explanation that no oxalic acid–β-CD interaction could be detected [4] by freezing point depression method.

In the series of normal aliphatic dicarboxylic acids, the two carboxylate groups are separated with a hydrocarbon chain, and the stability of the H-bond connecting them is inversely proportional to the size of the possible ring. As the data prove, the K_{d1}/K_{d2} value is greatest at oxalic acid, while it is negligible for adipic acid ($K_{d1}/K_{d2} \approx 6$, which nears the statistical probability [15]). Among the acids investigated, diethyl malonic acid has the greatest difference between the two acidic dissociation steps ($K_{d1}/K_{d2} \approx 3 \times 10^4$), presumably because of the steric effect of the two ethyl substituents. (It can be mentioned that some other substituted malonic acids have similar or higher K_{d1}/K_{d2} ratios [19].)

The special intramolecular H-bond renders a very compact structure ready for inclusion into the CD cavity. The better inclusion is promoted indirectly by the intramolecular H-bond of the guest, thereupon the HA^- species of dicarboxylic acids with intramolecular H-bond are assumed to form more stable inclusion complexes with CD than either the linear HA^- or the uncharged H_2A species. This assumption is suggested by the fact that hydrogen maleate and hydrogen malonate ions form inclusion complexes with α-CD of unusual stability [13].

In the series investigated, β-CD generally form more stable complexes with the undissociated acids than with their deprotonated derivatives, and a continuous increase in stability constants is noticed in the homologous series with increasing chain length. The strongly hydrated dianions do not form inclusion complexes, except in the

Table 1. Stability constants of 1:1 complexes of dicarboxylic acids with β-CD

Dicarboxylic acid	K^a_{d1}	K^b_{d2}	K^c_{211}	K^d_{111}	K^e_{011}
Oxalic acid	$(1.48 \pm 0.29) \times 10^{-1}$	$(1.70 \pm 0.19) \times 10^{-4}$	4.2 ± 0.1	[n]	[n]
Malonic acid	$(2.20 \pm 0.24) \times 10^{-3}$	$(6.36 \pm 0.85) \times 10^{-6}$	8.1 ± 0.1	[n]	[n]
Succinic acid	$(1.03 \pm 0.19) \times 10^{-4}$	$(4.92 \pm 0.52) \times 10^{-6}$	17.5 ± 0.2	6.6 ± 0.2	[n]
Glutaric acid	$(9.74 \pm 0.81) \times 10^{-5}$	$(1.27 \pm 0.20) \times 10^{-5}$	54.2 ± 0.5	10.5 ± 0.2	[n]
Adipic acid	$(5.91 \pm 0.46) \times 10^{-5}$	$(1.01 \pm 0.25) \times 10^{-5}$	113.2 ± 1.3	33.1 ± 0.8	9.6 ± 0.7
Diethyl malonic acid	$(6.05 \pm 0.88) \times 10^{-3}$	$(1.83 \pm 0.15) \times 10^{-7}$	324.3 ± 2.7	127.0 ± 1.4	5.5 ± 1.8
Fumaric acid	$(2.14 \pm 0.37) \times 10^{-3}$	$(8.83 \pm 0.81) \times 10^{-5}$	53.6 ± 0.6	12.3 ± 0.2	4.2 ± 0.5
Maleic acid	$(2.04 \pm 0.26) \times 10^{-2}$	$(1.84 \pm 0.21) \times 10^{-6}$	18.2 ± 0.1	31.5 ± 0.7	7.1 ± 0.5

[a] $K_{d1} = \frac{[H^+][HA^-]}{[H_2A]}$; [b] $K_{d2} = \frac{[H^+][A^{2-}]}{[HA^-]}$; [c]see Equation (5); [d]see Equation (4); [e]see Equation (3); [n]: uncertain.

case of adipate, where the relatively long hydrophobic chain (coiled up to some extent) is able to fill the β-CD cavity. Despite this, the values of formation constants are lower than those for α-CD [13], which means that these species have a less tight fit into the larger cavity of β-CD.

The data of Table 1 show that the hydrogen maleate ion is unique, since this HA^- species forms a more stable inclusion complex with β-CD than the corresponding dicarboxylic acid. As discussed, hydrogen maleate ion has an unusually strong intramolecular hydrogen bond, and the resulting six membered ring provides a better fit into the cavity of β-CD. (Maleic acid and its saturated equivalent, succinic acid, form inclusion complexes of similar stabilities, but the stability of the β-CD–hydrogen succinate inclusion complexes is lower, since the H-bonded hydrogen succinate ring is less stable as a result of the free rotation around the C–C bond.)

Comparing the stability constants of fumaric, maleic and succinic acids, that of the fumaric acid is surprisingly high. The straight *trans* structure of fumaric acid allows for no *intramolecular* hydrogen bonding, but its increased ability to form *intermolecular* hydrogen bonds seems very probable, resulting from the rigid structure that keeps the carboxylic groups just within a favourable distance for H-bonding with the OH-groups of the β-CD rims. (Since the stability of the β-CD–hydrogen fumarate is about double that of the hydrogen succinate, not only the proton donating action of the carboxylic group, but also the proton accepting role of the carboxylate can be assumed.)

Diethyl malonic acid forms the most stable inclusion complex among the investigated acids. The stability constant K_{211} nears those of aromatic compounds and is forty times higher than that of the malonic acid. (This difference must be connected to the more bulky groups with the apolar surface interacting well with the cavity of β-CD.) Contrary to our expectations, the inclusion complex formation constant of its half dissociated species does not exceed that of the undissociated acid. (The explanation can be that the complex formation is dominated by the inclusion of the bulky apolar part, but the remarkably high K_{111}/K_{011} ratio makes the importance of the β-CD·HA^- species very probable.)

Sometimes *formation of mixed ternary complexes* has also been detected in the course of the spectrophotometric investigations, and their presence may increase the number of equilibria, e.g. with methyl orange:

$$H_2A + D + M \Leftrightarrow D \cdot M \cdot H_2A \quad \beta_{2111} = \frac{[D \cdot M \cdot H_2A]}{[H_2A][D][M]} \tag{21}$$

which is manifested in a trend of the calculated equilibrium constants as a function of increasing acid concentration (inexplicable using different sets of acceptable q–r values). Using Equation (21), the concentration of the assumed ternary complex can be expressed:

Table 2. Stability constants of ternary complexes

Phenolphthalein (K_{0111})			Methyl orange (K_{2111})	
Malonate	Glutarate	Fumarate	Maleic acid	Fumaric acid
1.37 ± 0.12	6.79 ± 0.25	2.70 ± 0.15	2.93 ± 0.20	19.9 ± 1.2

$$[D \cdot M \cdot H_2A] = \beta_{2111}[H_2A][D][M] \tag{22}$$

and adding this species to Equation (19), the computer calculations produced very good results.

The H_2A:β-CD:M ratio is 1:1:1 in the ternary complexes of methyl orange, and the A^{2-}:β-CD:Ph ratio is also 1:1:1 in those of phenolphthalein.

The equilibrium constants are given in Table 2. It appears as if the unsaturated acids prefer the ternary complex formation. At present, we do not want to discuss these phenomena in detail.

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