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Microscopic Acid Dissociation Constants of 3,4-Dihydroxyphenylbutyric Acid and 3,4-Dihydroxybenzoic Acid

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The two phenol ionizations of 3,4-dihydroxyphenylbutyric acid and 3,4-dihydroxybenzoic acid were studied by detailed potentiometric titration and complementary tristimulus colorimetric method (CTS method). The thermodynamic parameters were calculated from the dissociation constants. From a comparison of the related compounds of 3,4-dihydroxyphenylbutyric acid, it was indicated that the effect of carboxylate group on the dissociations of two phenol groups was not present when more than two methylene groups were introduced between benzene ring and carboxylate group.

The microscopic acid dissociation constants of 3,4-dihydroxyphenylbutyric acid and 3,4-dihydroxybenzoic acid were calculated by two different methods. In Method A, the dissociation constants of 3-methoxy-4-hydroxyphenyl derivatives were used as substituted values. Method B is a modification of Edsall method. There were no effect of carboxylate group on the tautomeric constants when more than one methylene group are introduced between benzene ring and carboxylate group.

Keywords——3,4-dihydroxyphenylbutyric acid; 3,4-dihydroxybenzoic acid; titration; CTS method; dissociation constant; micro-constant

The ionization equilibria of many compounds which contain both two adjacent phenols and substitution groups (catechol derivatives) have been the subject of many works,[2,3,4] since the relative contribution of each of these groups to the dissociation of the two phenol-protons can not be determined unequivocally. Namely, a decision between these alternative is very difficult owing to the absence of a reliable method which would permit a distinction between the differently ionized forms. In order to know a detailed dissociation phenomenon of a compound which has several dissociable group in itself, it is necessary to know the numerical values of both the dissociation constants and the microscopic acid dissociation constants (micro-constants). Recently we have succeeded in determining all twelve micro-constants for 3,4-dihydroxyphenylalanine (DOPA)[5] and 3,4-dihydroxyphenethylamine (Dopamine).[6] The present paper deals with the acid dissociation phenomena of 3,4-dihydroxyphenylbutyric acid, 3,4-dihydroxybenzoic acid and the related compounds. These compounds seemed to us important enough to warrant detailed study, because the present result was used in the determination of the micro-constants for DOPA. Therefore, this paper makes not only a ground for the determination of the micro-constants of DOPA but also makes the supplement for the previous reports.[5]

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2) R.F. Jameson and M.F. Wilson, *J. Chem. Soc.*, **1972**, 2610.

3) H. Harada, *Nippon Kagaku Zasshi*, **90**, 267 (1969).

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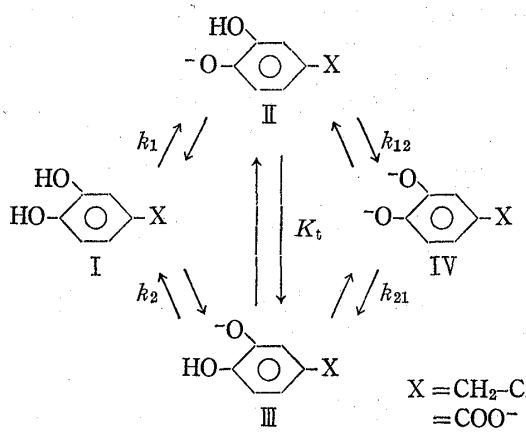
Experimental

Materials——3,4-Dihydroxyphenylbutyric acid and 3-methoxy-4-hydroxyphenylbutyric acid were synthesized by the method of Yamada, *et al.*[7] and Gaslini, *et al.*[8] respectively. 3-Methoxy-4-hydroxybenzoic acid and catechol were purchased from Nakarai Chemical Co., Kyoto and were used without further purification. All other materials were of analytical reagent grade.

pH Titration and Measurement of Absorption Spectra——The pH titration and the measurement absorption spectra were carried out by using the same apparatus as described previously.[5] The 5×10^{-3} M solution of the compound was titrated with carbonate-free 0.1 M potassium hydroxide. The titrations were done at temperatures of 1°, 15°, 25°, 35°, and 45° (all $\pm$ 0.1°). The spectra of compounds at 25° were measured at a concentration of 2×10^{-4} M. The pH of the solution and ultra-violet absorption were simultaneously measured after all the solutions were prepared and mixed under an oxygen free nitrogen atmosphere. The ionic strength of the solution was adjusted to 0.1 with sodium perchlorate.

Determination of Dissociation Constants——The dissociation constants of the compounds were calculated according to the three methods, titration-method of Schwarzenbach,[9] Complementary Tristimulus method (CTS method),[10,11] and Method B.[5]

Determination of Micro-constants——The acid dissociation of the catechol derivatives is expressed as shown in Chart 1. The micro-constants of 3,4-dihydroxyphenylbutyric acid and 3,4-dihydroxybenzoic acid were obtained by the following two methods.



$$K_1 = k_1 + k_2 \quad (1)$$

$$K_2^{-1} = k_{12}^{-1} + k_{21}^{-1} \quad (2)$$

$$K_1K_2 = k_1k_{12} = k_2k_{21} \quad (3)$$

$$K_t = \frac{k_2}{k_1} = \frac{k_{12}}{k_{21}} \quad (4)$$

Chart 1. Scheme of Ionization Equilibrium of Catechol Derivatives

Method A[12,13]——In Chart 1, the dissociation constants of 3-methoxy-4-hydroxyphenyl derivatives were expediently used as the value of k_1, which corresponds to the dissociation of the *p*-phenol group.

Method B——The calculations were performed as described previously.[5]

Results and Discussion

The dissociation constants of the catechol derivatives are listed in Table I. The pK_1 and pK_2 values of these compounds correspond to the dissociation of phenol groups, and pK_{COOH} to those of carboxyl group. From Table I, the following can be concluded. The pK_1 values of four catechols increased with increasing methylene group between benzene ring and carboxyl group. This trend was also observed in pK_2 values of 4-hydroxyphenyl-, 4-hydroxy-3-methoxyphenyl-, and 3-hydroxyphenyl-derivatives.[5] It is well known that a carboxylate group on the benzene ring introduces a pronounced electron-withdrawing effect on para-position.[4] This effect is observed in the pK_1 values of 3,4-dihydroxybenzoic acid, 3-methoxy-

7) F. Yamada and S. Matsuda, *Kogyo Kagaku Zasshi*, **59**, 59 (1956).
8) F. Gaslini and L.Z. Nahum, *J. Org. Chem.*, **29**, 1177 (1964).
9) G. Schwarzenbach, *Helv. Chim. Acta*, **33**, 947 (1950).
10) H. Flaschka, *Talanta*, **7**, 90 (1960).
11) S. Hirose, I. Ikeuchi, and K. Sakakibara, *Bunseki Kagaku*, **21**, 183 (1972).
12) J.T. Edsall, R.B. Martin, and B.R. Hollingworth, *Proc. Natl. Acad. Sci., U.S.A.* **44**, 505 (1958).
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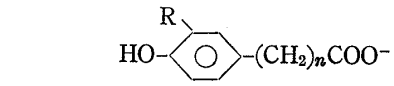
Table I. Dissociation Constants of 3,4-Dihydroxyphenylbutyric Acid and Its Related Compounds

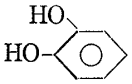
Compound R	Compound n	Titration method pK_{COOH}	Titration method pK_1	Titration method pK_2	CTS method pK_1	CTS method pK_2	Method B pK_1	Method B pK_2
OH	0	4.40±0.04	8.93±0.03	11.70±0.05[5]	8.89±0.03	11.73±0.07	8.81±0.04	11.82±0.05
	1[5]	4.22±0.02	9.58±0.02	12.15±0.03	9.61±0.04	12.03±0.02	9.57±0.05	11.98±0.04
	2[5]	4.47±0.01	9.69±0.02	12.11±0.04	9.76±0.03	11.99±0.02	9.74±0.06	12.08±0.05
	3	4.38±0.02	9.72±0.03	12.18±0.04	9.81±0.04	12.09±0.03	9.76±0.05	12.13±0.04
OCH_3	0	4.39±0.01	9.06±0.02		8.97±0.04			
	1[5]	4.42±0.02	9.87±0.02		9.88±0.03			
	2[5]	4.59±0.03	9.98±0.02		10.04±0.04			
	3	4.27±0.03	10.01±0.03		10.03±0.04			
H	0	4.47±0.01	9.06±0.03[5]		8.99±0.04			
	1[5]	4.36±0.02	9.99±0.01		9.96±0.05			
	2[5]	4.50±0.03	10.14±0.03		10.13±0.03			
	3	4.21±0.02	10.15±0.02		10.07±0.03			
3,4-dihydroxy			9.49±0.03	12.06±0.04	9.56±0.04	12.04±0.03		

4-hydroxybenzoic acid, and 4-hydroxybenzoic acid. However, Table I indicates that the electron-withdrawing effects of carboxylate group are weakened increasing methylene groups. There is no more the effect of carboxylate group on the dissociations of two phenol groups when more than two methylene groups are introduced between benzene ring and carboxlate group. The pK_2 values gave reasonably high values in 3,4-dihydroxyphenylbutyric acid and 3,4-dihydroxybenzoic acid, suggesting that the pK_2 values of the three catechols are not influenced by both the methylene groups and carboxylate group. The thermodynamic parameters and the plots of ΔH against $T\Delta S$ for the first phenol and the second phenol dissociation of the phenol and catechol derivatives are shown in Table II and Fig. 1, respectively. The second

Table II. Thermodynamic Parameters for Ionization of Phenols at 25°

Compound	ΔG_1 (kcal/mol)	ΔG_2 (kcal/mol)	ΔH_1 (kcal/mol)	ΔH_2 (kcal/mol)	ΔS_1 (e.u.)	ΔS_2 (e.u.)
3,4-dihydroxyphenylbutyric acid	13.26	16.61	6.48	9.31	−22.75	−24.50
4-hydroxyphenylbutyric acid	13.78		6.31		−25.07	
4-hydroxyphenylacetic acid	13.63		6.15		−25.10	
3-methoxy-4-hydroxyphenylbutyric acid	13.65		6.24		−24.88	
3-methoxy-4-hydroxyphenylpropionic acid	13.61		6.14		−25.07	
3-methoxy-4-hydroxyphenylacetic acid	13.46		6.10		−24.70	
3-methoxy-4-hydroxybenzoic acid	12.36		3.44		−29.93	



Compound R	Compound n	Number
OH	0	1
	1[5]	2
	2[5]	3
	3	4
OCH_3	0	5
	1	6
	2	7
	3	8
H	0[5]	9
	1	10
	2[5]	11
	3	12
		13[2]

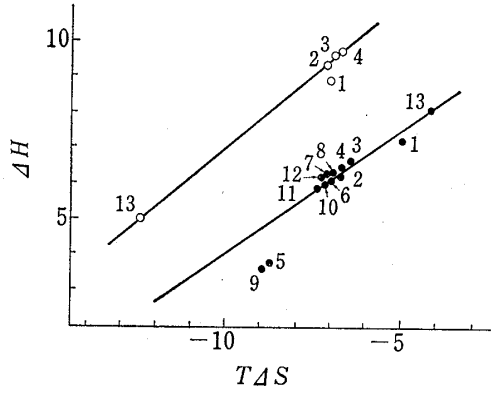
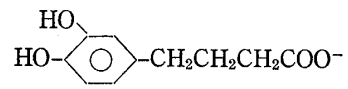
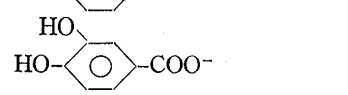


Fig. 1. Relationship Between ΔH and $T\Delta S$ for Phenolic-type Ionization of 3,4-Dihydroxyphenylbutyric Acid and Its Related Compounds

—●—, first phenol ionization; —○—, second phenol ionization.

phenol ionization of catechols gave a different linear-correlation than the first phenol ionization, probably due to the formation of an intramolecular hydrogen bond after the dissociation of the first phenol group. Therefore, the dissociation constants of methoxyphenol derivatives can be used satisfactorily for the value of k_1 (in Chart 1) in the calculation of the micro-constants of 3,4-dihydroxyphenylbutyric acid, while there is no hydrogen bonding effect in the first ionizations of the catechols. To obtain detailed information about the dissociation of 3,4-dihydroxyphenylbutyric acid, the micro-constants were calculated by two different method, as was reported previously.[5] The micro-constants and tautomeric constant (K_t) are listed in Table III. The concentration ratio of the two intermediates, represented by the

Table III. Microscopic Acid Dissociation Constants and Tautomeric Constants of 3,4-Dihydroxyphenylbutyric Acid and 3,4-Dihydroxybenzoic Acid

Compound	Method	k_1	k_2	k_{12}	k_{21}	K_t
	A	10.01[a]	10.03	11.89	11.87	0.96
	B	10.02±0.02	10.06±0.03	11.86±0.03	11.79±0.02	0.91
	A	9.06[b]	9.51	11.57	11.11	0.35
	B	9.05±0.02	9.42±0.03	11.57±0.03	11.37±0.02	0.42

a) Dissociation constants of 3-methoxy-4-hydroxyphenylbutyric acid (10.01±0.03).
b) Dissociation constants of 3-methoxy-4-hydroxybenzoic acid (9.06±0.02).

tautomeric constants, show a definite trend and are 0.35, 0.94,[5] 0.95,[5] and 0.96 (by comparison of method A) for 3,4-dihydroxybenzoic acid (n=0), 3,4-dihydroxyphenylacetic acid (n=1), 3,4-dihydroxyphenylpropionic acid (n=2), and 3,4-dihydroxyphenylbutyric acid (n=3), respectively. These values indicate that in 3,4-dihydroxybenzoic acid the first ionization occurs predominantly on the 4-phenol, while in the other three catechol derivatives the proton dissociates approximately equally from the 3- and 4-phenols. The carboxylate group seems to have no effect on the tautomeric constants when more than one methylene group are introd-

uced between benzene ring and carboxylate group. This assumption was successfully used in the determination of the micro-constants for DOPA.[5] By use of these micro-constants the relative concentrations of various ionic forms of the compounds were calculated as a function of pH, and the results are shown in Fig. 2 and Fig. 3, respectively.

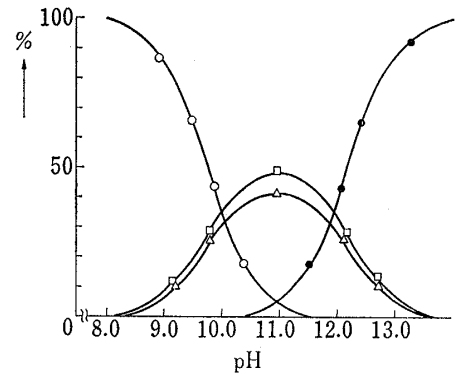


Fig. 2. Relative Concentration of Various Ionic Forms of 3,4-Dihydroxyphenylbutyric Acid

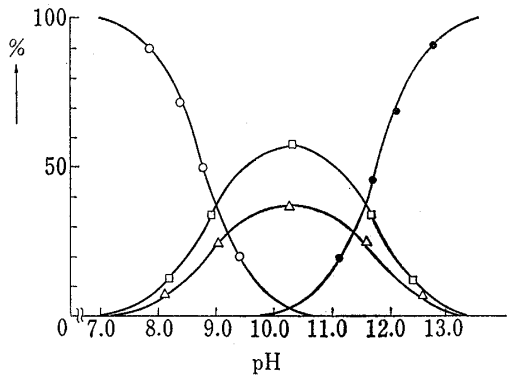


Fig. 3. Relative Concentration of Various Ionic Forms of 3,4-Dihydroxybenzoic Acid