Catalytic Activities of Salicylaldehyde Derivatives. VIII. Kinetic Studies of the Catalytic Racemization of L-Glutamic Acid at 25 °C

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The racemization of L-glutamic acid catalyzed by 15 kinds of salicylaldehyde derivatives has been kinetically studied at 25 °C and pH 10 in the presence of copper(II) ion. When 4- and 5-substituted salicylaldehydes were used as the catalyst, Hammett's plots for the racemization against σ^- were found to be linear with fewer points deviating from the line than the plots against σ. This fact has not been observed previously, since the salicylaldehyde derivatives tested having a substituent of different value between σ and σ^- were degraded during the course of reaction at 80 °C. Hammett's plots for the reaction catalyzed by 3-substituted salicylaldehydes indicated no linear relation with either σ or σ^-. These catalytic racemizations, including the case of the 6-substituted salicylaldehydes have been discussed.

In previous papers,[1–4] the racemization of L-glutamic acid catalyzed by various salicylaldehyde derivatives has been kinetically studied in the presence of copper(II) ion at pH 10 and 80 °C. Eighty degrees has been adopted as the temperature in order to observe the slow catalytic racemization throughout these studies. Hammett's plots for the racemization catalyzed by 4- and 5-substituted salicylaldehydes indicated a linear relation against Hammett's constant, σ.[2,3] It was difficult sometimes to determine the observed rate constants for the catalytic racemization of some salicylaldehyde derivatives such as the dimethylsulfonio derivatives, because of degradation of the catalysts at 80 °C.[4,5]

This paper deals with the determination of the observed rate constants, k_{obsd}, for the catalytic racemization at 25 °C and with the relation between $\log k_{\text{obsd}}$ and Hammett's constant. The following 15 salicylaldehyde derivatives were used as the catalysts: salicylaldehyde (SAL), 3-bromo- (3-BR), 5-bromo- (5-BR), 3-nitro- (3-NI), 4-nitro- (4-NI), 5-nitro- (5-NI), 6-nitro-salicylaldehyde (6-NI), 3-trimethylammonio- (3-TA), 4-trimethylammonio- (4-TA), 5-trimethylammonio- (5-TA), 6-trimethylammonio- (6-TA), 3-dimethylsulfonio- (3-DS), 4-dimethylsulfonio- (4-DS), 5-dimethylsulfonio- (5-DS), and the 6-dimethylsulfonio-derivative of salicylaldehyde (6-DS).

As described previously,[1–4] the catalytic racemization of L-glutamic acid has been carried out in the presence of copper(II) ion (L-glutamic acid: copper(II) ion: the catalyst=1: 0.02: 0.02 in molar ratio) at pH 10 and 25 °C, under which conditions no side reaction such as transamination was observed. Since it is well documented that the catalytic racemization obeys a first-order kinetic law, the catalytic activity, $(\log \alpha_0 - \log \alpha_t)/t$, should be a constant, where t is the time and α_t is the observed optical rotation at t. The observed rate constant, k_{obsd}, has been calculated from the following equation:

$$k_{\text{obsd}} = \frac{2.30 \times (\log \alpha_0 - \log \alpha_t)}{t}.$$

Experimental

Preparation of the Catalysts. Commercially available SAL was purified by vacuum distillation. 3-BR,[2] 5-BR,[2] 3-NI,[2] 4-NI,[6] 5-NI,[2] 6-NI,[7] 3-TA,[3] 4-TA,[1] 5-TA,[3] 6-TA,[8] 3-DS,[5] 4-DS,[5] 5-DS,[5] and 6-DS[4] were prepared by methods described in the literature.

Procedure of the Racemization.[1] In a tightly stoppered test tube a mixture of a pH-adjusted solution (pH 10, 2 ml) of sodium L-glutamate (2 mmol) containing copper(II) sulfate (0.04 mmol) and a pH-adjusted 0.05 M borate buffer solution (pH 10, 2 ml) of the catalyst (0.04 mmol) was kept at 25 °C for the required time. After the reaction time as described in Table 1, 6 M hydrochloric acid (5 ml) was added to the mixture in order to stop the reaction. The optical rotation of the resulting solution was measured with a Perkin-Elmer model 141 polarimeter (direct reading, 0.001° with an error of ±0.002°; $\alpha_0 = +1.02°$).

Results and Discussion

As Table 1 shows, the mode of the catalytic activity may be classified into three categories according to the kind of the catalyst used; in the first case, the catalytic activity is nearly constant throughout the reaction (SAL, 3-BR, 5-BR, 3-NI, 5-NI, 3-TA, 4-TA, 5-TA, 3-DS, and 5-DS); in the second one, it is approximately constant only at the early stage of the reaction and then gradually falls (4-NI, 6-TA, 4-DS, and 6-DS); in the last case, it lacks constancy even at the early stage of the reaction (6-NI). The decrease in the catalytic activity has been accompanied by a simultaneous decrease in the absorption maximum of the reaction mixture at *ca.* 380 nm, which has been attributed to the chelation of the Schiff base of glutamic acid with the catalyst and copper(II) ion,[9] as previously reported.[3,10] From these constant values of the catalytic activities, the observed rate constants, k_{obsd}, have been calculated as shown in Table 2. For comparison, k_{obsd} for the reaction catalyzed by pyridoxal has also been calculated from the data in Ref. 10.

It has been found that the plots of $\log k_{\text{obsd}}$ against Hammett's constant, σ,[11] were on a straight line for the reaction catalyzed by SAL, 5-BR, 5-NI, 4-TA, 5-TA, and 5-DS except 4-NI and 4-DS. In the cases of 4-NI and 4-DS, $\log k_{\text{obsd}}$ were abnormally large against the corresponding σ.

As Fig. 1 shows, the plots of $\log k_{\text{obsd}}$ against Hammett's constant, σ^-,[12] indicate a linear relation for all of the 4- and 5-substituted salicylaldehydes

Table 1. Catalytic activity at 25 °C

Time h	Catalytic activity $(\log \alpha_0 - \log \alpha_t) \times 10^5/t$, (min^{-1})														
	SAL	3-BR	5-BR	3-NI	4-NI	5-NI	6-NI	3-TA	4-TA	5-TA	6-TA	3-DS	4-DS	5-DS	6-DS
2					26.7								22.9		20.9
4					29.5		11.4					10.5	23.9	14.3	21.2
6					29.6								23.3		22.0
8				8.06	26.6	9.10	10.5	4.64	10.2	10.7	6.74	11.6	23.5	14.1	21.1
16				8.13	16.6	9.11	8.6	4.72	10.4	11.0	6.80	11.1	22.5	14.2	19.6
24	1.57	3.71	3.92	8.25	11.3	8.73	7.4	4.44	10.1	10.8	6.67	11.4	21.6	14.0	18.5
32				8.14	8.6	8.47	6.8	4.54	10.3	10.8	5.98	11.1	21.3	13.1	16.9
40				8.05	7.4	8.37	6.2	4.59	10.2	10.8	6.28	10.9	21.0	13.7	16.3
48	1.68	3.70	3.79	7.93	6.4	8.50	5.9	4.52	10.2	10.8	6.06	11.0	19.9	13.5	16.1
72	1.59	3.61	3.62	7.73	4.5	8.44	5.0	4.69	10.1	10.8	5.61	11.2	18.8	13.9	14.8
96	1.59	3.59	3.89	7.81	3.8	8.13	4.3	4.67	10.1	10.6	5.22	10.9	17.5	13.5	14.5
120	1.62	3.63	3.76	7.57	3.3	8.10	3.9	4.66	10.0	10.7	5.08	10.7	17.3	13.2	13.6
168	1.67	3.47	3.61	7.77	2.8	8.10	3.2	4.57	9.8	10.3	4.84	10.7	15.6	13.3	11.8
240	1.58	3.45	3.68												
360	1.57	3.34	3.60												
480	1.57	3.33	3.64												

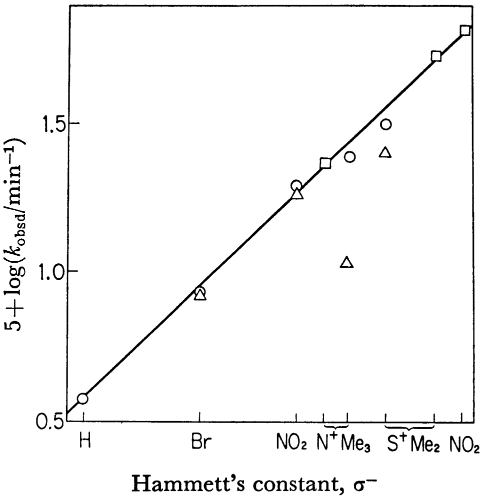


Fig. 1. Relation between the obsd rate const, k_{obsd}, and Hammett's const, σ^-.
△: 3-, □: 4-, ○: 5-substituted salicylaldehyde.

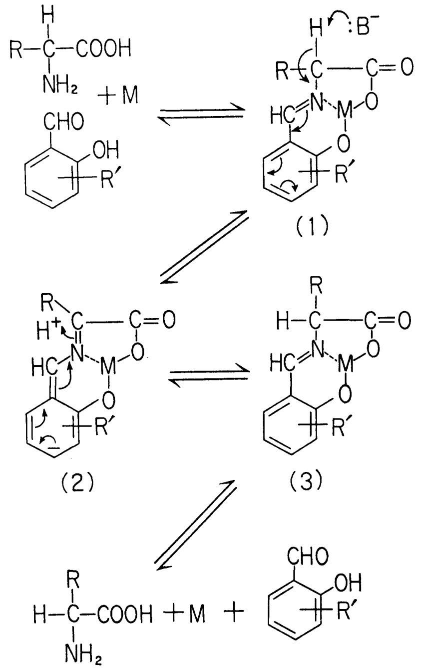
tested including 4-NI and 4-DS. The reaction constant, ρ, has been determined as 0.99. As it has been well documented, σ^- is determined by the ionization constants of substituted phenols or anilines, whereas σ is based on the ionization constants of substituted benzoic acids. Therefore the σ^--values of some substituents such as *p*-nitro and *p*-dimethylsulfonio groups, which can conjugate with hydroxyl or amino groups through quinonoidal-conjugate rings, are considerably larger than the corresponding σ-values. This means that Hammett's constants of *m*- and *p*-substituents such as trimethylammonio group having a negligible quinonoidal-conjugate effect are of no difference between σ and σ^-, since there are two cases, whether the σ^--value includes only an electron-withdrawing effect or a combination of electron-withdrawing and conjugate effects. Probably, this conjugate effect is expected to act between formyl group and nitro or dimethylsulfonio group in the para position on the benzene ring.

The Braunstein-Snell mechanism for non-enzymatic reactions of amino acids catalyzed by pyridoxal in the presence of a metal ion[13)] has been generally accepted. When the mechanism is applied to the salicylaldehyde system, the presence of the intermediates, **1**, **2**, and **3** shown in Scheme have to be considered. The contribution of a substituent such as *p*-nitro or *p*-dimethylsulfonio group to the resonance of the quinonoidal form conjugated with a formyl group would stabilize **2**, resulting in an increase in the rate of racemization. Consequently, it is reasonable that in the cases of 4-NI and 4-DS, Hammett's plots against σ^- are linear although those against σ are not.

Table 2. Observed rate constant, k_{obsd}

	k_{obsd}, (min^{-1})		k_{obsd}, (min^{-1})
SAL	3.7×10^{-5}	5-TA	24.7×10^{-5}
3-BR	8.4	6-TA	14.8
5-BR	8.6	3-DS	25.3
3-NI	18.2	4-DS	53.8
4-NI	65.4	5-DS	31.5
5-NI	19.6	6-DS	49.0
3-TA	10.6		
4-TA	23.3	pyridoxal	64.8

As shown in Table 2, The observed rate constants for 5-substituted salicylaldehydes are larger than those for the corresponding 3-isomers in spite of having the same σ^--value. Possibly, the 3-substituents sterically hinder the formation of the chelate ring of the adjacent phenol group with copper(II) ion. Similar phenomena have also been observed at 80 °C.[2,3)] The differences in k_{obsd} between 3-TA and 5-TA and 3-DS and 5-DS are considerably larger than those between other 3- and 5-substituted salicylaldehydes. Apparently 3-TA, 5-TA, 3-DS, and 5-DS have a bulky and positively charged substituent, therefore, in the racemization by 3-TA and 3-DS, the formation of the chelate ring is inhibited and this is assumed due to the effects of simple steric hindrance and additional strong ionic repulsion



between the substituent and copper(II) ion.

Since steric effects of the 6-substituents on the adjacent formyl group would not be straightforward and Hammett's constants of the *o*-substituent have not been determined, the evaluation of Hammett's constant of an *o*-substituent based on the racemization catalyzed by 6-substituted salicylaldehyde has not been attempted. The larger catalytic activities of 6-NI and 6-DS compared to the corresponding 5-isomers are thought due to a similar case of *p*-substituents of 4-NI and 4-DS.

As Table 1 shows the orders of the catalytic activities at the early stage of the reaction are 4-NI>6-NI>5-NI>3-NI, 4-DS>6-DS>5-DS>3-DS, and 5-TA>4-TA>6-TA>3-TA. As described above, this order is reasonable qualitatively considering the electron-withdrawing effect, the resonance effect through the conjugate system, and the steric hindrance of a substituent including ionic repulsion. These results show that the steric effect of the 3-substituent on the phenol group seems to be larger than that of the corresponding 6-substituent on the formyl group and that the formation of the chelate ring of the hydroxyl group in the salicylaldehyde with copper(II) ion plays an important role in the catalytic racemization.

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