BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 2628—2631 (1969)

Catalytic Activities of Salicylaldehyde Derivatives. II. Kinetic Studies of the Racemization of Amino Acid

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(Received February 14, 1969)

In the racemization reaction of L-glutamic acid, catalyzed by salicylaldehyde derivatives and cupric ions, the rate constants, k, of 3-bromo-, 3-methoxy-, 3-methyl-, 3-nitro-, 4-methyl-, 5-bromo-, 5-methoxy-, 5-methyl-, and 5-nitro-salicylaldehydes and of salicylaldehyde were measured and the kinetic relation between the rate constant, k, of the salicylaldehyde derivatives and the corresponding Hammett's constant, σ, was studied. A linear relation between log k and the σ of 4- or 5-substituted salicylaldehydes and another linear relation between log k and the σ of 3-substituted salicylaldehydes were found. The activation energies of the racemizations catalyzed by pyridoxal, 3-nitro-, and 5-nitro-salicylaldehydes and by salicylaldehyde were determined, but no distinct difference between 3-nitrosalicylaldehyde and 5-nitrosalicylaldehyde was observed.

It has been reported that, in the racemization of sodium L-glutamate at pH 10 and at 80°C, 4-formyl-3-hydroxyphenyltrimethylammonium bromide, which is a salicylaldehyde derivative substituted by one of the strongest electron-attracting groups, has the most effective catalytic activity.[1] Yoshikawa *et al.*[2] have stated that the order of the racemization yield of L-glutamic acid catalyzed by nitro-, sulfo-, and sulfonamide-derivatives of salicylaldehyde agreed with the order of Hammett's constant, σ. The p-trimethylammonium group has a larger value based on the ionization of substituted benzoic acids than those of the corresponding nitro-, sulfo-, and sulfonamide groups.[3] This paper will deal with the kinetic relation between the catalytic activity of various salicylaldehyde derivatives and Hammett's constant, σ, of the corresponding substituents.

The activation energy of racemization catalyzed by 3-nitro- and 5-nitro-salicylaldehydes, salicylaldehyde, and pyridoxal was also studied.

Experimental

Preparation of Catalysts. 3-Bromo-,[4] 5-bromo-,[5] 4-dimethylamino-,[6] 3-methyl-,[7] 4-methyl-,[8] 5-methyl-,[9] 5-methoxy-,[10] 3-nitro-,[11] and 5-nitro-salicylaldehydes,[11] 4-formylphenyltrimethylammonium iodide,[12] 4-formyl-3-hydroxyphenyltrimethylammonium bromide,[1] and pyridoxal[13] were prepared by the method described in the literature.

Procedure of Racemization. Racemization was carried out as has been described before.[1] All the reactions were performed at pH 10 according to precedent. To 2 m*l* of a solution in a tightly-stoppered test tube containing sodium L-glutamate (2 mmol) and cupric sulfate (0.04 mmol) (pH 10), 2 m*l* of a borate buffer solution (pH 10) of a catalyst (0.04 mmol) were added; the mixture was reacted at the mentioned temperature for the mentioned time. When the required temperature was below room temperature, each solution was cooled for 1 hr at that temperature before mixing. After the required reaction time, 5 m*l* of 6N hydrochloric acid were added and the optical rotation of the solution $[\alpha_t]$ was measured by a Perkin-Elmer model 141 polarimeter (direct reading, 0.001°). The racemization yield was calculated as follows:

$$100([\alpha_0] - [\alpha_t])/[\alpha_0]$$

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Results and Discussion

Effect of the Kind of Substituent of Benzaldehyde. The *o*-hydroxyl group in benzaldehydes must play a crucial role in the catalytic activity of racemization, and an electron-attracting substituent on the benzene ring promotes the activity.[2] In order to verify the effects of various kinds of substituents on racemization, several salicylaldehydes and benzaldehydes were carefully examined. The results are listed in Table 1, which shows

Table 1. Comparison of racemization yields by aldehydes in the presence of cupric ion

Subst. BzH				Racemi. yield
2-	3-	4-	5-	
OH	H	NMe_3Br	H	85.4%
OH	H	H	NO_2	82.7
OH	NO_2	H	H	70.6
OH	H	H	Br	62.2
OH	Br	H	H	54.9
OH	H	H	OMe	44.0
OH	OMe	H	H	40.1
OH	H	H	H	39.2
OH	H	H	Me	34.0
OH	H	Me	H	31.3
OH	Me	H	H	28.3
OH	H	OH	H	14.8
OH	H	NMe_2	H	7.5
OMe	H	H	H	7.1
H	H	NMe_2	H	3.2
H	H	NMe_3I	H	2.0
	no catalyst			2.2

Aldehyde (0.04 mmol), cupric sulfate (0.04 mmol), and L-glutamic acid (2 mmol) were used and reacted at 80°C for 3 hr.

that no benzaldehyde derivatives except *o*-methoxybenzaldehyde showed any activity of racemization. The activity of salicylaldehyde derivatives which were substituted by electron-releasing groups was weaker than that of derivatives substituted by electron-attracting groups and that of salicylaldehyde itself. Moreover, the racemization yield of 3-substituted salicylaldehyde was lower than that of the corresponding 5-isomer.

Relation between the Rate Constant, k, and Hammett's Constant, σ. The rate constant of the racemization of sodium L-glutamate in the presence of cupric ions and catalyzed by salicylaldehyde derivatives was studied. The rate constant was calculated as follows:

$$kt = 2.30 \times (\log [\alpha_0] - \log [\alpha_t])$$

where k is the rate constant, t is the time, and $[\alpha_t]$ is the observed rotation at t. The rate constant of racemization catalyzed by 4-formyl-3-hydroxyphenyltrimethylammonium bromide at 80°C has been described previously.[1] The activities of 3-bromo-, 5-bromo-, 3-methoxy-, 5-methoxy-, 3-methyl-, 4-methyl-, 5-methyl-, 3-nitro-, and 5-nitrosalicylaldehydes and salicylaldehyde were also measured at 80°C. However, within 2 or 3 hr the catalytic activity of 3-bromo-, 5-bromo-, and 3-nitro-salicylaldehydes was gradually lowered, probably because of the decomposition of these catalysts. The plots indicating the first-order reaction are shown in Fig. 1, from which rate con-

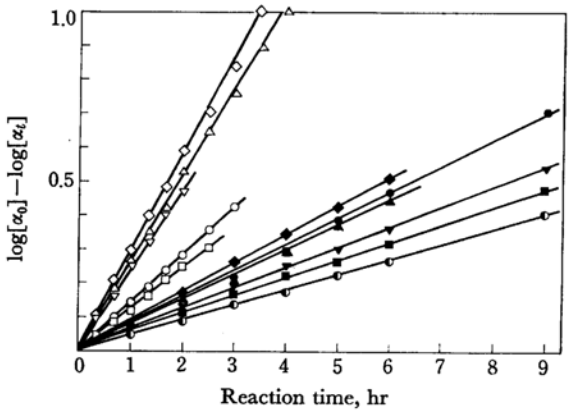


Fig. 1. Catalytic activities of salicylaldehyde derivatives at 80°C in the presence of cupric ion.
◇ 4-Trimethylammonium, △ 5-Nitro, ▽ 3-Nitro, ○ 5-Bromo, □ 3-Bromo, ◆ 5-Methoxy, ▲ 3-Methoxy, ● Salicylaldehyde, ▼ 5-Methyl, ■ 4-Methyl, ◐ 3-Methyl.

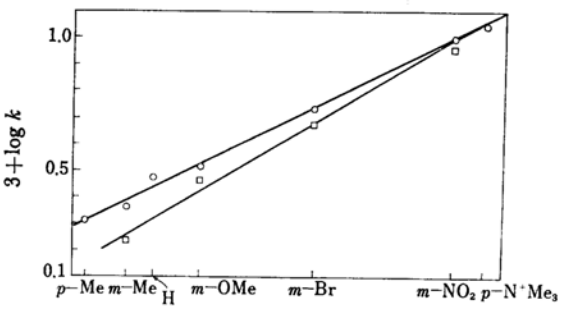
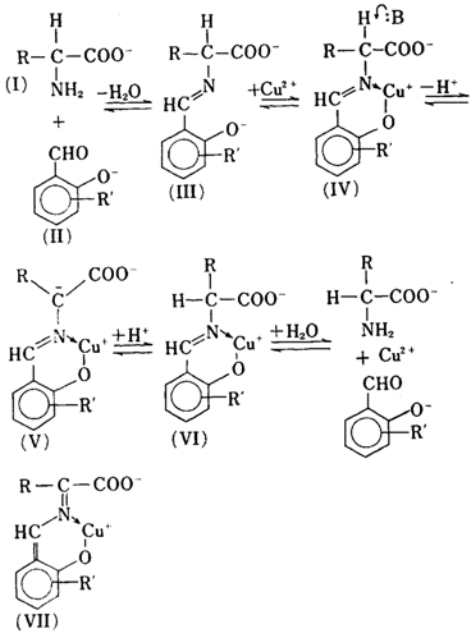


Fig. 2. Relation between rate constant k and Hammett's constant σ.
○ 4- or 5-Substituted salicylaldehydes.
□ 3-Substituted salicylaldehydes.

stants, k, were calculated. In Fig. 2 log k is plotted against Hammett's constant, σ.[3] As Fig. 2 shows, the rate constants of 5-substituted salicylaldehydes were larger than those of the corresponding 3-isomers, probably because of some ortho steric effect in the formation of the chelate ring (IV), though the structure of the chelate complex around the copper has not yet been satisfactorily clarified.

A linear relation between log k and Hammett's constant, σ, of 4- or 5-substituted salicylaldehydes, and an another linear relation between log k and the σ of 3-substituted salicylaldehydes, were observed; the reaction constants were 0.76 and 0.91 respectively.



Snell[14] reported that, in a Schiff's base (III) of pyridoxal and amino acid, the α-carbon atom of amino acid was conjugated with the nitrogen atom of the pyridine ring and that consequently the α-proton of amino acid was eliminated easily and a racemization reaction occurred. However, Pullman[15] pointed that the conjugated system was only extended to the nitrogen atom of amino acid; before the transition state the α-carbon atom did not belong to the conjugated system. Yoshikawa[2] discussed how the electron-withdrawing power of the nitrogen atom of amino acid was activated by the inductive effect of the substituted benzene ring.

Since our results showed that the rate constant of the catalytic racemization by substituted salicylaldehydes obeyed Hammett's rule, the rapid formation of aldimine (III, IV) and the decrease in electron density around the nitrogen atom of the stabilized aldimine-chelate system should be caused mainly by inductive and mesomeric effects. Thus, the α-carbon of amino acid, affected by partial positively-charged aldimine nitrogen, would be readily converted to carbanion (V) by basic catalysis.

The negligible transamination together with the racemization of the glutamic acid catalyzed by 4-formyl-3-hydroxyphenyltrimethylammonium bromide[1] suggest that the *p*-trimethylammonium group should be unfavorable to the formation of a conjugated system with ketimine (VII)[2] from carbanion (V).

Activation Energy of Racemization, Catalyzed by 3-Nitro-, 5-Nitro-salicylaldehydes, Salicylaldehyde, and Pyridoxal Hydrochloride. Because the rate constant of 5-nitrosalicylaldehyde was larger than that of 3-nitrosalicylaldehyde, the

Table 2. The rate constants of 3-nitrosalicylaldehyde, 5-nitrosalicylaldehyde, salicylaldehyde and pyridoxal hydrochloride at various temperatures

Temp. °C	k ($\times 10^{-3}$ min^{-1})			
	3-NO_2	5-NO_2	Sal.	Pyr.
100		26.1	9.21	
90		15.8	5.44	
80	9.12	10.0	3.01	
70	5.21	5.76	1.53	
60	2.79	3.09	0.728	
50	1.45	1.55	0.351	3.92
40	0.712	0.745	0.146	2.08
30				1.04
20	0.138	0.136		0.483
0				0.0980

Aldehyde (0.04 mmol), cupric sulfate (0.04 mmol), and L-glutamic acid (2 mmol) were used.

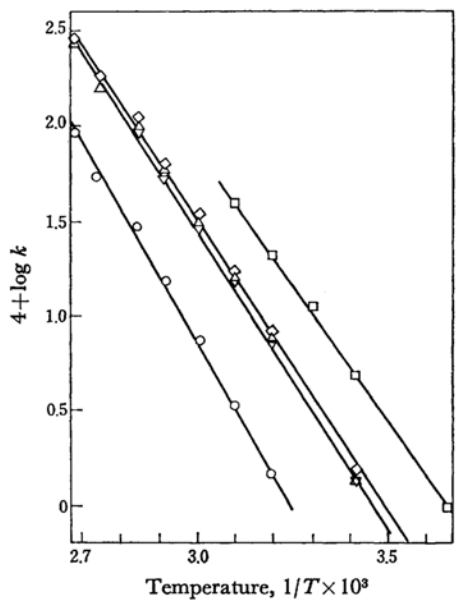


Fig. 3. Effect of temperature on rate constant.
□ Pyridoxal, ◇ 4-Formyl-3-hydroxyphenyltrimethylammonium bromide, △ 5-Nitrosalicylaldehyde, ▽ 3-Nitrosalicylaldehyde, ○ Salicylaldehyde.

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activation energies might differ from each other as a result of the ortho steric effect on the hydroxyl group. The rate constants of 3-nitro-, 5-nitrosalicylaldehydes, salicylaldehyde, and pyridoxal hydrochloride were measured at various temperatures. At 80°C pyridoxal did not satisfy the first-order reaction, as has previously been described,[1] but below 50°C our results followed the first-order reaction equation at first. At temperatures higher than 90°C, as compared with the catalytic activity of 5-nitrosalicylaldehyde, that of 3-nitrosalicylaldehyde was lowered very much as time passed, probably because of its decomposition, but the rate constant was measured only below 80°C. The rate constants are summarized in Table 2. The linear relations observed between log k and $1/T$ are shown in Fig. 3. Because the line of 3-nitrosalicylaldehyde almost overlapped with that of the 5-isomer, so that they could not be distinguished from each other, the line of the 3-isomer was omitted from Fig. 3. The activation energies of pyridoxal, 5-nitrosalicylaldehyde, 3-nitrosalicylaldehyde, and salicylaldehyde were 13.0 kcal/mol, 14.3 kcal/mol, 14.4 kcal/mol, and 16.0 kcal/mol respectively. The activation energy of 4-formyl-3-hydoxyphenyltrimethylammonium bromide was 14.3 kcal/mol.[1] Pyridoxal has the least activation energy and the largest rate constant, and it was the best catalyst for racemization, but, as has been established before, at high temperatures the catalytic activity was lowered as time passed. No distinct difference in activation energy was observed between 5-nitrosalicylaldehyde and 3-nitrosalicylaldehyde.