FORMATION AND STABILITY OF AMIDE AND IMIDE LINKS

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T. V. Sheremeteva and V. A. Gusinskaya

Institute of Macromolecular Compounds, Academy of Sciences of the USSR
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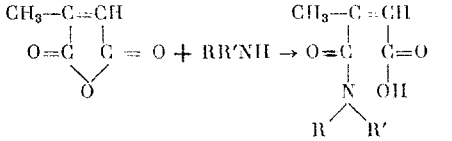
It has been shown previously [1, 2] by a comparison of the cyclization of N-alkylcitraconamic acids [N-alkyl-2- or 3-methylmaleamic acids] with the reactions of aniline and of amino acids with citraconic anhydride with formation of N-substituted citraconimides in one stage that in the first case temperatures of 140-220°C are required for reaction [3, 4], whereas in the second and third cases temperatures of 80 to 100°C are sufficient. The ease with which aniline and amino acids are acylated is to be explained by the mobility of the hydrogen atoms of the amino group due to the presence of electron-acceptor substituents on the nitrogen atom.

We here report a further study of this reaction. We planned to separate the process of the formation of N-(carboxymethyl)- and N-aryl-citraconimides into the formation of the amides and the intramolecular imidation, to determine the hydrolytic stability of the amide link in citraconamic acids when the possibility of cylization is removed by the introduction of a second substituent on the nitrogen atom, and finally to study the formation of N-derivatives of citraconimide by the acylation of weakly basic amines, e.g., p-nitroaniline.

N-Substituted citraconamic acids were synthesized as follows:



where R = C_6H_5, $C_6H_4NO_2$, CH_3; R' = H, CH_3, C_2H_5

For the study of the hydrolytic stability of the amide link, as well as N-aryl and N-(carboxymethyl) derivatives we synthesized N-alkyl-N-aryl, N,N-dialkyl, and N-p-nitrophenyl derivatives. N-p-Nitrophenylcitraconamic acid was also used in the study of the formation of N-p-nitrophenylcitraconimide. N-Aryl-, N,N-dialkyl-, and N-alkyl-N-aryl-citraconamic acids were prepared by adding the amine slowly to a solution of citraconic anhydride in an organic solvent (benzene, ether, or acetone). The results of the experiments are given in Table 1. We were unable to prepare N-(carboxymethyl) citraconamic acid by this method because of the insolubility of glycine in organic solvents. We prepared this dibasic acid by the hydrolytic cleavage of N-(carboxymethyl)citraconimide [citraconimidoacetic acid] with aqueous alkali.

When two moles of potassium hydroxide was added to one mole of N-(carboxymethyl)citraconimide, the dark-red coloration characteristic for imides in alkaline solution appeared, but then rapidly disappeared. This indicated the opening of the imide ring with formation of the N-(carboxymethyl)citraconamic acid dipotassium salt.

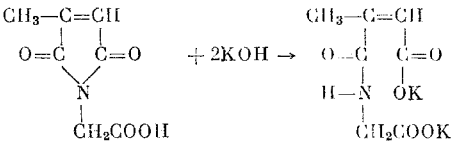
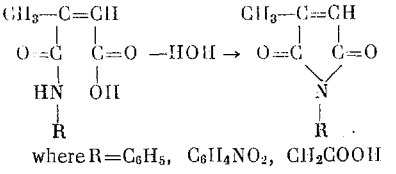


TABLE 1. Preparation of N-Substituted Citraconamic Acids

Amide	Reactants, moles		Solvent	Reaction temp., °C	Yield, %	Mol. wt.		M.p., °C	N, %		Solvent crystallization
	citraconic anhydride	amine				tit.*	calc.		found	calculated	
N,N-Dimethylcitraconamic acid	0.1	Dimethylamine (gaseous), 0.1	Benzene	25	59.5	157	157	105	8.97	8.92	Acetone
N-Ethyl-N-phenylcitraconamic acid	0.1	N-Ethylaniline, 0.1	Ether	25	82.0	233	233	108	6.0	6.0	Ethanol
N-Phenylcitraconamic acid	0.15	Aniline, 0.15	The same	20	87.5	204.5	205	170	6.75	6.82	Ethanol-acetone, 1:1
N-p-Nitrophenylcitraconamic acid	0.15	p-Nitroaniline	Acetone	25	77.4	250	250	159	5.63	5.6	The same

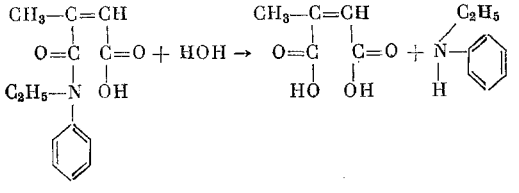
*tit is the mol. wt. by titration with 0.1 N NaOH.

For the preparation of N-(carboxymethyl)citraconamic acid the potassium ions were displaced by the addition of an equimolecular amount of sulfuric acid. We were unable to isolate N-(carboxymethyl) citraconamic acid from aqueous solution because of the ease with which cyclization occurred. Its dipotassium and disilver salts were isolated and characterized.



The cyclization of all the N-substituted citraconamic acids except the N-p-nitrophenyl derivative was conducted in aqueous solution by refluxing them or heating them in sealed tubes at 100-110°C. The formation of an imide ring was shown by a qualitative test (red coloration on addition of alkali). N-p-Nitrophenylcitraconamic acid is sparingly soluble in water. Boiling it in aqueous suspension led to the hydrolysis of the amide link. In this case cyclization was conducted in alcoholic solution with and without the absorption of reaction water (to suppress hydrolysis) by means of phosphorus pentoxide. The imides formed were extracted from the reaction mixtures with organic solvents, from which they were then isolated by crystallization in a freezing mixture. The rate of cyclization was determined from the rate at which the acidity of the reaction mixture diminished.

To avoid the formation of a stable five-membered imide ring, the hydrolytic stability of the amide link was studied for N,N-disubstituted citraconamic acids, for which cyclization is impossible. We found that in aqueous solution at 100°C the hydrolysis of N-ethyl-N-phenylcitraconamic acid with formation of citraconic acid goes to the extent of 90% in 15 h.



Under these conditions N,N-dimethylcitraconamic acid is not hydrolyzed.

EXPERIMENTAL

N-Ethyl-N-phenylcitraconamic Acid. 12.1 g of N-ethylaniline was added slowly with stirring to a solution of 11.2 g of citraconic anhydride in 50 ml of ether at 20-25°C, and the reaction mixture was stirred for 2-3 h at this temperature. The precipitate of N-ethyl-N-phenylcitraconamic acid was filtered off and recrystallized from alcohol. N-Phenyl-, N-p-nitrophenyl-, and N,N-dimethylcitraconamic acids were prepared analogously (see Table 1).

Dipotassium and Disilver Salts of N-(Carboxymethyl)citraconamic Acid. A solution of 2.24 g of KOH in 8 ml of water was added to 3.38 g of N-(carboxymethyl)citraconimide at room temperature. The solution obtained was evaporated almost to dryness. The precipitate was washed with alcohol. We obtained 3.69 g (70.4%) of the dipotassium salt. After recrystallization from aqueous alcohol N-(carboxymethyl)citraconamid acid dipotassium salt formed a white crystalline substance, m.p. 203-204°C. Found %: N 5.37; C 31.79; H 2.82. $C_7H_7O_5NK_2$. Calculated %: N 5.32; C 31.93; H 2.66.

The disilver salt was prepared from the dipotassium salt by the action of silver nitrate solution. The white precipitate formed was recrystallized from water; yield 92%. Found %: Ag 53.71. $C_7H_7O_5NAg_2$. Calculated %: Ag 53.8.

Cyclization of N-(Carboxymethyl)citraconamic Acid. 0.098 g of H_2SO_4 (about 1 ml of 2 N solution) was added to 0.26 g of the dipotassium salt (the solution was neutral). This solution was sealed in a tube and heated at 100°C for 16 h. The presence of an imide ring in the reaction product was indicated by a red coloration when the contents of the tube were made alkaline. From the reaction mixture with hot benzene we isolated 0.09 g (53.3%) of N-(carboxymethyl)citraconimide, which was precipitated when the solution was cooled m.p. 127°. Found %: N 8.27; mol. wt. 168.5 (titration). $C_7H_7O_4N$. Calculated %: N 8.28; mol. wt. 169. For the original N-(carboxymethyl)citraconimide we found: m.p. 126°; N 8.28; mol. wt. 168 (titration). A mixture melted without depression.

Determination of Rate of Cyclization. A solution of 2.24 g of KOH in 4 ml of water was added to 3.38 g of N-(carboxymethyl)citraconimide. When the pink color had disappeared 3.4 ml of 12 N H_2SO_4 was added. The solution was diluted to 25 ml with water in a measuring flask. 3-ml portions of this solution were introduced into a number of tubes, which were sealed and placed in a thermostat at 100°C. After a period of 4, 8, 12, or 16 h from the start of the reaction the contents of one of the tubes were titrated with 0.1 N NaOH to determine the amount of N-(carboxymethyl)citraconimide formed in the reaction, i.e., the rate of cyclization was determined from the reduction in the acidity of the reaction mixture. On the basis of the experimental data a graph was constructed (see Fig. 1) for the relation of the amount of cyclization to time.

Cyclization of N-Phenylcitraconamic Acid. 2.05 g of N-phenylcitraconamic acid in 30 ml of water was refluxed for 16 h. On cooling, N-phenylcitraconimide was precipitated in white needles; weight 1.6 g; m.p. 98° (from ether). Cyclization went to the extent of 88%. Found %: N 7.07. $C_{11}H_9O_2N$. Calculated %: N 7.15.

The rate of cyclization of N-phenylcitraconamic acid was determined from the diminution in the acidity of the reaction mixture with time. The experiment was conducted as follows: in each of a number of tubes a mixture of 0.16 g of N-phenylcitraconamic acid and 0.4 ml of 1:1 aqueous alcohol was prepared. The tubes were sealed and placed in a thermostat at 100-110°C. After 4, 8, 12, or 16 h the contents of one of the tubes was titrated with 0.1 N NaOH. From the diminution in the acidity of the reaction mixture the extent of the conversion of the amic acid into the imide was calculated. The results of the experiments are shown in a graph (see Fig. 1). It will be seen that in the course of 16 h cyclization goes to the extent of 87%.

Cyclization of N-p-Nitrophenylcitraconamic Acid. 0.3 g of N-p-nitrophenylcitraconamic acid in 25 ml of water was refluxed for 16 h. On cooling, 0.12 g of a yellow precipitate, m.p. 146°, was formed. Found %: N 20.32. $C_6H_6O_2N_2$. Calculated %: N 20.28.

The melting point and analysis corresponds to p-nitroaniline, and a mixture with known p-nitroaniline melted without depression. Hence, under these conditions N-p-nitrophenylcitraconamic acid is not cyclized, but is hydrolyzed to p-nitroaniline and citraconic acid. In the course of 16 h the reaction goes to the extent of 72.6%.

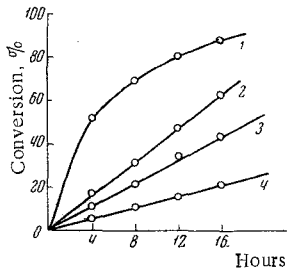


Fig. 1

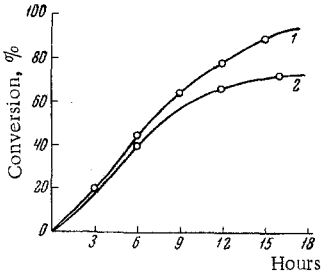


Fig. 2

Fig. 1. Rate of cyclization of citraconamic acids into imides: 1) N-phenyl; 2) N-(carboxymethyl); 3) N-p-nitrophenyl in presence of P_2O_5; 4) N-p-nitrophenyl.
Fig. 2. Rate of hydrolysis of 1) N-ethyl-N-phenylcitraconamic acid; 2) N-p-nitrophenylcitraconamic acid.

To effect the cyclization on N-p-nitrophenylcitraconamic acid the reaction was conducted in an alcoholic instead of an aqueous medium. 0.5 g of the amic acid in 1.0 ml of alcohol was introduced into a tube, which was sealed and heated in a thermostat at 110°C for 16 h. The contents of the tube were transferred to a flask, diluted with 5 ml of alcohol, and cooled strongly. We obtained 0.104 g of a white crystalline product, m.p. 153-154° (from alcohol). Found %: N 12.36; C 57.20; H 3.4. $C_{11}H_8O_4N_2$. Calculated %: N 12.07; C 56.90; H 3.44. The analysis corresponded to N-p-nitrophenylcitraconimide. Cyclization went to the extent of 22.8%.

With the object of suppressing hydrolysis, the cyclization of N-p-nitrophenylcitraconamic acid was conducted in presence of phosphorus pentoxide to remove water from the sphere of reaction. 0.5 g of the amic acid in 1.0 ml of alcohol was introduced into a test tube, which was placed in a larger glass tube containing phosphorus pentoxide. This tube was sealed and placed in a thermostat at 100-110°C for 16 h. The contents of the test tube were then transferred to a flask, diluted with 5 ml of alcohol, and cooled strongly. We isolated 0.216 g of N-p-nitrocitraconimide, m.p. 153°C. In this case cyclization went to the extent of 47%.

The rate of cyclization of N-p-nitrophenylcitraconamic acid was determined from the diminution in the acidity of the reaction mixture with time. For this purpose 0.16 g of the amic acid in 0.4 ml of alcohol was introduced into each of a number of test tubes, which were placed in larger tubes containing phosphorus pentoxide, which were sealed. The assemblies were placed in a thermostat at 100-110°C. After 4, 8, 12, or 16 h the contents of one of the test tubes were titrated with 0.1 N NaOH to determine the rate of the conversion of the amic acid into the imide. The results of the experiments are presented in Fig. 1. It will be seen from the figure that in presence of phosphorus pentoxide cyclization goes to the extent of 44% in 16 h, but in absence of the desiccant it goes to the extent of 22.1% in the same time. In the latter case the experiment was conducted analogously.

Hydrolysis of N-Ethyl-N-phenylcitraconamic Acid. 0.2 g of N-ethyl-N-phenylcitraconamic acid in 2 ml of water was introduced into each of a number of tubes. The tubes were sealed and left in a thermostat at 100°C. After 3, 6, 9, 12, or 15 h from the start of the reaction the contents of one of the tubes were titrated with 0.1 N NaOH. The rate of hydrolysis was determined from the increase in the acidity of the reaction mixture. For each case the amount of citraconic acid formed in the hydrolysis was calculated. The results are shown in Fig. 2. In the course of 16 h hydrolysis went to the extent of 63%. In an attempt to hydrolyze N,N-dimethylcitraconamic acid under analogous conditions the starting substance was recovered. The amounts of alkali consumed in the titration of samples taken before and after the experiment were the same.

DISCUSSION OF EXPERIMENTAL RESULTS

Our experiments show that, when various N-substituted citraconamic acids are heated, two competing reactions are possible: cyclization of the amic acid to the corresponding imide as a result of intramolecular elimination of water, and hydrolysis of the amide link with formation of citraconic acid and the original amine. The stability of the amide link to hydrolysis and also the mobility of the hydrogen atoms on the nitrogen depend on the character of the N-substituent. The more marked the electron-

acceptor properties of the substituent, the less stable and more readily hydrolyzed the amide link and the more mobile the hydrogen atoms on the nitrogen. In the case of citraconamic acids derived from weak bases such as p-nitroaniline ($K_b = 1.24 \cdot 10^{-13}$) heating in aqueous solutions results mainly in hydrolysis (to the extent of 72% in 16 h at 100°C). The cyclization of N-p-nitrophenylcitraconamic acid is only possible when the process is conducted in alcoholic solution (the reaction goes to the extent of 22% in the course of 16 h at 100°C; see Fig. 1). The rate and extent of the process increase when the reaction water is removed from the sphere of reaction. Thus, in presence of phosphorus pentoxide for 16 h at 100°C 44% of the amic acid is converted into the imide.

The cyclization of citraconamic acids derived from more highly basic amines such as glycine (K_b $2.6 \cdot 10^{-12}$) and aniline (K_b $5.4 \cdot 10^{-10}$) in aqueous solution at 100-110°C goes to a greater extent (63 and 88% respectively). In this case the reversibility of the process due to hydrolysis is suppressed by the formation of a fairly stable imide ring.

When the possibility for cyclization is removed by the introduction of a second substituent on the nitrogen atom, an alkylarylamide link is readily hydrolyzed at 100°C, whereas a dialkylamide link remains unchanged under the same conditions. The low mobility of the hydrogen atom in N-alkylcitraconamic acids is responsible for the necessity for a higher temperature (140-200°C) in the cyclization of these amic acids.

CONCLUSIONS

1. The following previously undescribed substances were prepared and characterized: the dipotassium and disilver salts of N-(carboxymethyl)citraconamic acid, N-p-nitrophenylcitraconamic acid, and N-p-nitrophenylcitraconimide.

2. When aqueous solutions of N-arylcitraconamic acids are heated at 80-100°C, two competing reactions occur: cyclization into imides and hydrolysis of the amide link. The predominance of one or the other reaction depends on the basicity of the amine from which the amic acid is derived.

LITERATURE CITED

1. T. V. Sheremeteva, T. Yu. Stolyarova, and G. N. Larina, Izv. AN SSSR, Otd. khim., n, 1961, 1681.
2. A. Piutti, Gazz. Chim. Ital., 126, 431 (1896).
3. T. V. Sheremeteva and G. N. Larina, Izv. AN SSSR, Otd. khim., n, 1959, 843.
4. I. Gottlieb, Liebigs Ann. Chem., 77, 269 (1851).