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Regioselectivity in the Catalytic Hydrogenolysis of 1-Amino-1-cyclopropanecarboxylic Acid and Its Methyl Ester

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The title compounds were hydrogenolyzed over Pd-C. The ring-bond cleavage in the hydrogenolysis of the acid in water or methanol occurred at both the C_1–C_2 bond and the C_2–C_3 bond in nearly equal proportion, whereas the C_1–C_2 bond was cleaved mainly in the presence of ammonia and the C_2–C_3 bond was cleaved mainly in acetic acid. Selective hydrogenolysis of the C_1–C_2 bond of ester occurred in hexane or methanol, whereas the C_2–C_3 bond was hydrogenolyzed mainly in acetic acid. The role of the amino group is discussed.

Although many studies on the regioselectivity in the catalytic hydrogenolysis of substituted cyclopropanes have been reported,[1] little attention has been given to the catalytic hydrogenolysis of aminocyclopropanes. Recently, Musso[2] reported that 1-amino-1-cyclopropanecarboxylic acid was hydrogenolyzed selectively at the opposite bond of the amino group in methanol in the absence or in the presence of ammonia by the use of a palladium catalyst. On the contrary, we found previously that *exo*-7-aminobicyclo[4.1.0]heptane and *exo*-6-aminobicyclo[3.1.0]hexane were hydrogenolyzed exclusively at the adjacent bond of the amino group in hexane using both palladium and nickel catalysts.[3] In order to make clear the role of the amino group which might cause these conflicting results, we have investigated the hydrogenolysis of methyl 1-amino-1-cyclopropanecarboxylate (**1**) and 1-amino-1-cyclopropanecarboxylic acid (**2**) in neutral, basic or acidic solution.

Table 1. Hydrogenolysis of Methyl 1-Amino-1-cyclopropanecarboxylate (**1**)

Run No.	Solvent	Conversion %	Composition of products/%		
			C_2–C_3 Fission		C_1–C_2 Fission
			3	**4**	**5**
1[a]	Hexane	0	—	—	—
2[b]	Hexane	64	—	2	98
3[a]	CH_3OH	0	—	—	—
4[b]	CH_3OH	28	17	—	83
5[a]	CH_3COOH	28	84	12	4

Substrate: 58 mg, 0.5 mmol. Catalyst: Pd-C, 50 mg. Reaction time: 24 h. a) Room temperature, atmospheric pressure. b) 80°C, 50 kg cm^{-2}.

The hydrogenolysis of **1** and **2** was carried out by the use of palladium-charcoal (Pd-C) catalyst and the results are shown in Tables 1 and 2.

The hydrogenolysis of **1** was made easy by increasing the reaction temperature and the hydrogen pressure. The hydrogenolysis of **1** in hexane gave selectively methyl 2-aminobutanoate (**5**) as the C_1–C_2 bond cleaved product, accompanied by a slight amount of methyl 2-amino-2-methylpropanoate (**4**) as the C_2–C_3 bond cleaved product. The hydrogenolysis of **1** in methanol also gave mainly **5**, accompanied by a small amount of methy 2-methylpropanoate (**3**) as the C_2–C_3 bond cleaved product. On the other hand, when acetic acid was used as a solvent, selective hydrogenolysis of the C_2–C_3 bond of **1** occurred at

Table 2. Hydrogenolysis of 1-Amino-1-cyclopropanecarboxylic Acid (**2**)

Run No.	Solvent	Conversion %	Composition of products/%[g]		
			C_2–C_3 Fission		C_1–C_2 Fission
			3	**4**	**5**
6[a]	H_2O	100	28	17	55
7[a]	H_2O-NH_3[c]	86	9	3	88
8[a]	H_2O-CH_3COOH[d]	93	88	4	8
9[a]	CH_3OH	100	49	3	48
10[a]	CH_3OH-NH_3[e]	93	9	—	91
11[b]	CH_3COOH[f]	18	14	78	8
12[b]	CH_3COOH	17	86	14	—

Substrate: 100 mg (1 mmol). Catalyst: Pd-C, 200 mg. Solvent: 10 ml. Reaction time: 24 h. a) 100 °C, 80 kg cm^{-2}. b) Room temperature, atmospheric pressure. c) NH_3 is contained in amounts eight times the molar quantity of **2**. d) CH_3COOH is contained in amounts ten times the molar quantity of **2**. e) NH_3 is contained in amounts five times the molar quantity of **2**. f) PtO_2 (50 mg) is used instead of Pd-C. g) Products were determined as methyl esters.

Table 1. Hydrogenolysis of Methyl 1-Amino-1-cyclopropanecarboxylate (**1**)

Run No.	Solvent	Conversion %	Composition of products/%		
			C_2–C_3 Fission		C_1–C_2 Fission
			3	**4**	**5**
1[a]	Hexane	0	—	—	—
2[b]	Hexane	64	—	2	98
3[a]	CH_3OH	0	—	—	—
4[b]	CH_3OH	28	17	—	83
5[a]	CH_3COOH	28	84	12	4

Substrate: 58 mg, 0.5 mmol. Catalyst: Pd-C, 50 mg. Reaction time: 24 h. a) Room temperature, atmospheric pressure. b) 80°C, 50 kg cm^{-2}.

Table 2. Hydrogenolysis of 1-Amino-1-cyclopropanecarboxylic Acid (**2**)

Run No.	Solvent	Conversion %	Composition of products/%[g]		
			C_2–C_3 Fission		C_1–C_2 Fission
			3	**4**	**5**
6[a]	H_2O	100	28	17	55
7[a]	H_2O-NH_3[c]	86	9	3	88
8[a]	H_2O-CH_3COOH[d]	93	88	4	8
9[a]	CH_3OH	100	49	3	48
10[a]	CH_3OH-NH_3[e]	93	9	—	91
11[b]	CH_3COOH[f]	18	14	78	8
12[b]	CH_3COOH	17	86	14	—

Substrate: 100 mg (1 mmol). Catalyst: Pd-C, 200 mg. Solvent: 10 ml. Reaction time: 24 h. a) 100 °C, 80 kg cm^{-2}. b) Room temperature, atmospheric pressure. c) NH_3 is contained in amounts eight times the molar quantity of **2**. d) CH_3COOH is contained in amounts ten times the molar quantity of **2**. e) NH_3 is contained in amounts five times the molar quantity of **2**. f) PtO_2 (50 mg) is used instead of Pd-C. g) Products were determined as methyl esters.

room temperature under atmospheric pressure to give **3** and **4**, accompanied by a slight amount of **5**.

The hydrogenolysis of **2** was carried out in water and the reaction products were converted into methyl esters to submit to vapor-phase chromatography (VPC). The ring-bond cleavage of **2** in water occurred at both the C_1–C_2 bond and the C_2–C_3 bond in nearly equal proportion, whereas the C_1–C_2 bond was cleaved mainly in the presence of aqueous ammonia and the C_2–C_3 bond was cleaved mainly in the presence of acetic acid. The results (Run No. 9, 10, and 11) obtained by the reinvestigation under the conditions reported by Musso[2] were analogous to that described above.

According to Musso's report,[2] the ratios of 2-amino-2-methylpropanoic acid and 2-aminobutanoic acid obtained in the hydrogenolysis of **2** using Pd–C in methanol, Pd–C in methanol–ammonia and Pt in acetic acid were reported, respectively, as follows: 90%, 10%; 98.5%, 1.5%; 23%, 77%. He explained the results on the basis of his proposal,[4] concerning the regioselective effect of substituents in the hydrogenolysis of cyclopropanes, in the following manner. The amino group plays as an electron-donating group in the neutral or the basic solvent and the hydrogenolysis occurs at the weakened C_2–C_3 bond preferentially, whereas the amino group plays as an electron withdrawing group in the acidic solvent and causes the C_1–C_2 bond cleavage mainly.

Contrary to his explanation, however, our finding suggests strongly that the amino group of **2** contributes mainly to the cleavage of the C_1–C_2 bond when the hydrogenolysis is carried out under the condition in which the amino group behaves as a free amine, whereas the C_2–C_3 bond cleavage is prefered under the condition in which the amino group forms an ammonium ion. Additionally, the C_2–C_3 bond cleavage was accompanied by the elimination of the amino group.

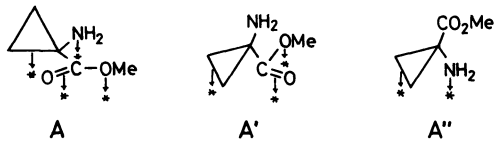
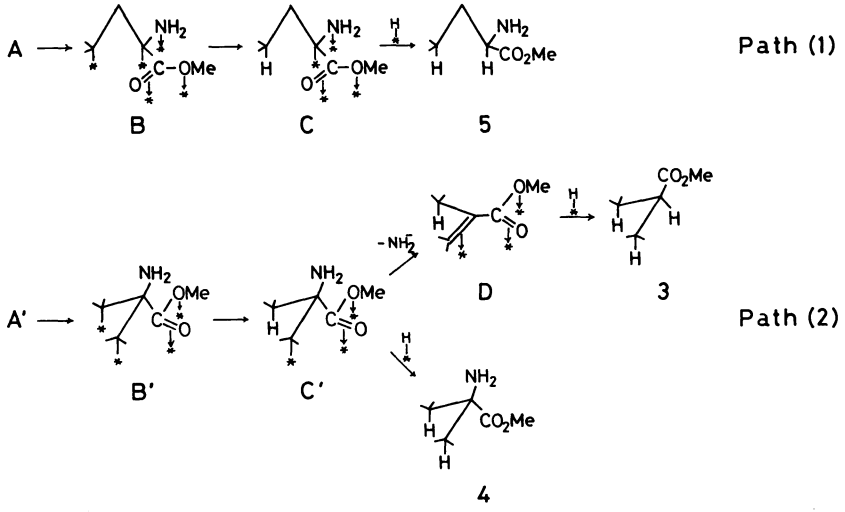


Fig. 1. Adsorbed states of **1** in neutral solvents.

The obtained results may be explained by considering the adsorbed states of **1** and **2** on the catalyst. The probable adsorbed states of **1** are shown in Fig. 1. The adsorbed state A which is adsorbed with the amino group, the methoxycarbonyl group and the C_1–C_2 bond of the cyclopropane ring seems to be preferable to A′ which is adsorbed with the methoxycarbonyl group and the C_2–C_3 bond or A″ which is adsorbed with the amino group and the C_2–C_3 bond. Therefore, it is expected that the predominant product is the C_1–C_2 bond cleaved product in the hydrogenolysis of **1** in the neutral solvent as shown in Path (1) in Scheme 1. The obtained results support this consideration.

A pathway of the formation of the minor products **3** and **4** is shown in Path (2) in Scheme 1. The C_2–C_3 bond cleavage of the adsorbed state A′ occurs more easily than that of the adsorbed state A″ because the unadsorbed amino group behaves as an electron-donating group and contributes to weakening the C_2–C_3 bond. The elimination of the amino group can be explained as an example of the elimination in the half-hydrogenated state.[5-8] In the half-hydrogenated state C′ formed from A′ via B′, the combination with the chemisorbed hydrogen competes with the elimination of the amino group caused by the donation of the electron of the carbon–metal bond to the C_1–C_2 bond. The tendency toward the elimination seems to be enhanced by the solvation of the leaving group with protic solvents such as methanol and water.

In the acidic solvent, the amino group of **1** is converted to ammonium ion and loses the ability of



Scheme 1.

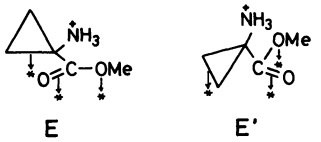


Fig. 2. Adsorbed states of **1** in acidic solvents.

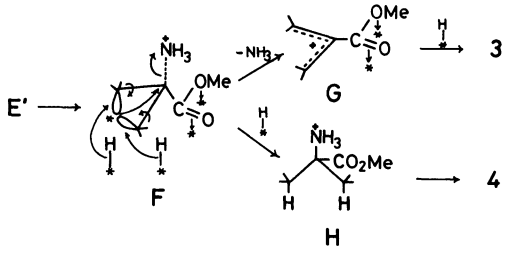
adsorption to the catalyst. Therefore, two forms of the adsorbed states E and E′, adsorbing with the methoxycarbonyl group and the C_1–C_2 bond or the C_2–C_3 bond, can be considered as shown in Fig. 2.

Although the hydrogenolysis of methyl cyclopropanecarboxylate has not been reported, it is expected that the C_1–C_2 bond is cleaved selectively because cyclopropyl methyl ketone is hydrognolyzed at the C_1–C_2 bond selectively.[9] If the ammonio group in **1** behaves as an electron withdrawing group and contributes to cleaving the adjacent C_1–C_2 bond as mentioned in Musso's proposal, it is expected that the combined influences of the ammonio and the methoxycarbonyl groups would cause the exclusive C_1–C_2 bond cleavage of **1**. On the contrary, the selective cleavage of the opposite C_2–C_3 bond and the elimination of the ammonio group were observed in our experiment. These results suggest that **1** is adsorbed mainly in the adsorbed state E′ and the hydrogenolysis proceeds according to the similar pathway shown in Path (2) in Scheme 1.

However, the hydrogenolysis of **1** in acetic acid proceeded more easily than in hexane or methanol and was accompanied by considerable elimination of the ammonio group. Therefore, it seems to be necessary to consider the relationship between the accelaration of the C_2–C_3 bond cleavage and the easy elimination of the ammonio group.

It is well-known that the accelerating effect in the solvolysis of cyclopropyl tosylates[10] or halides[11] is explained by the concept of σ-participation. In the adsorbed state E′, π-adsorption of the C_2–C_3 bond to the catalyst surface and the C–NH_3^+ bond are opposite in direction. Because the relationship in direction is preferable stereoelectronically, the acceleration of the hydrogenolysis in acidic solvent may be explained somewhat more clearly by the concept of the σ-participation. An increase of the polarization in C–NH_3^+ bond caused by the solvation makes the C_2–C_3 bond cleavage easy and the elimination of the ammonio group proceeds predominantly, competing with the combination of chemisorbed hydrogen as shown in Scheme 2.

Since the details of experimental conditions were not described in Musso's report, it is difficult to point out the cauces of discrepancies observed in the hydrogenolysis of **2**. However, the obtained results can be explained reasonably in the following manner. In aqueous solution, equilibrium is established among the dipolar ion of **2** and the anion and the



Scheme 2.

cation forms of **2**, whereas it is largely in the anion form in basic solution and largely in the cation form in acidic solution. Therefore, the composition of products in the hydrogenolysis of **2** in water is dependent on the equilibrium of the three forms of **2**. The anion form is adsorbed mainly with the C_1–C_2 bond, the amino group and the carboxyl group to give the C_1–C_2 bond cleaved product, whereas the dipolar ion and the cation form are adsorbed mainly with the C_2–C_3 bond and the carboxyl group to give the C_2–C_3 bond cleaved products being accompanied by the elimination of the ammonio group. The behavior of **2** in the hydrogenolysis in methanol, methanol–ammonia or acetic acid may be explained in a similar manner as above.

Experimental

Infrared spectra were recorded on a Hitachi 270-30 spetrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-PMX 60 spectrometer. Chemical shifts (δ) are recorded in ppm downfield Me_4Si.

1-Amino-1-cyclopropanecarboxylic Acid (2). **2** was prepared according to the method described in the literature.[12] To a solution of 1-[(diphenylmethylene)amino]-1-cyclopropanecarbonitrile, mp 77—80 °C, lit,[12] mp 77—80 °C, (7.5 g, 30.5 mmol) in ether (75 ml) was added 1 mol dm^{-3} hydrochloric acid (150 ml) and the mixture was stirred for 12 h at room temperature. The layers were separated and the aqueous layer was refluxed with concentrated hydrochloric acid (150 ml) for 4 h. After removal of the water, the residue was taken up in a small volume of water and passed through a column packed with weakly basic anion-exchange resin Bio-Rad AG3-X4A) to give 2.8 g of **2**: Mp 229—231 °C, lit,[12] mp 229—231 °C; ^{1}H NMR (D_2O)[12] δ=1.5 (2H, m, C<u>H</u>$_2$), 1.2 (2H, m, C<u>H</u>$_2$); IR(KBr) 1626 (ν_{COO^-}), 1538 ($\delta_{NH_3^+}$); Found: C, 47.36; H, 6.79; N, 13.97%. Calcd for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.85%.

Methyl 1-Amino-1-cyclopropanecarboxylate (1). To a solution of **2** (2.5 g, 24.8 mmol) in methanol (10 ml) was passed dried hydrogen chloride and refluxed for 12 h. After removal of the methanol the residue was made basic with diluted sodium carbonate solution and extracted with chloroform. The fractional distillation gave 0.6 g of **1**: Bp 45—47 °C/27 mmHg (1 mmHg=133.322 Pa); ^{1}H NMR (CCl_4) δ=3.60 (3H, s, OC<u>H</u>$_3$), 1.77 (2H, s, N<u>H</u>$_2$), 1.15 (2H, m, C<u>H</u>$_2$), 0.92 (2H, m, C<u>H</u>$_2$); IR (CCl_4) 3396 (ν_{NH}), 1724 ($\nu_{C=O}$), 1622 (δ_{NH}), 1192 (ν_{CO}); Found: C, 52.08; H, 7.92; N, 12.21%. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.16%.

Hydrogenolysis of 1. A solution of **1** (58 mg, 0.5 mmol) in hexane, methanol or acetic acid (5 ml) was stirred with Pd-C (50 mg, Kawaken Fine Chemical Co.: Pd-C(M)) at room temperature under hydrogen at atmospheric pressure or at 80 °C under hydrogen pressure of 50 kg cm^{-2} for 24 h. When hexane was used as a solvent, the reaction mixture was submitted directly to VPC to determine the composition of products. When methanol or acetic acid was used as a solvent, hexane (15 ml) was added to the reaction mixture and washed with water to remove the methanol or the acetic acid and submitted to VPC.

Hydrogenolysis of 2. A solution of **2** (100 mg, 1 mmol) in water (10 ml) in the absence or in the presence of aqueous ammonia (8 mmol) or acetic acid (10 mmol) was stirred with Pd-C (200 mg) at 100 °C under hydrogen pressure of 80 kg cm^{-2} for 24 h. After the catalyst and the water were removed from the reaction mixture, the residue was esterified with methanol in the presence of hydrogen chloride and submitted to VPC.

A solution of **2** (100 mg, 1 mmol) in methanol (10 ml) in the absence or in the presence of ammonia (5 mmol) was stirred with Pd-C (200 mg) at 100 °C under hydrogen pressure of 80 kg cm^{-2} for 24 h. The reaction mixture was esterified in a similar manner as above and submitted to VPC.

A solution of **2** (100 mg, 1 mmol) in acetic acid (10 ml) was stirred with Pd-C (200 mg) or PtO_2 (50 mg) at room temperature under hydrogen at atmospheric pressure for 24 h. The reaction mixture was esterified with methanol and submitted to VPC.

Identification of Products. The products were identified by comparison with ^{1}H NMR, IR spectra and the values of T_R in VPC of authentic samples prepared by the esterification of the corresponding carboxylic acids in the usual way.

Methyl 2-Methylpropanoate (3): Bp 92—93 °C, lit,[13] bp 91.5 °C/742 mmHg; ^{1}H NMR (CCl_4) δ=3.16 (3H, s, $OC\underline{H}_3$), 2.73—2.27 (1H, m, J=7.0 Hz, C$\underline{H}$), 1.14 (6H, d, J=7.0 Hz, $C\underline{H}_3$×2); IR (CCl_4) 1736 ($\nu_{C=O}$), 1200 (ν_{CO}), 1156 (ν_{CO}).

Methyl 2-Amino-2-methylpropanoate (4): Bp 132—134 °C, lit,[14] bp 133—134 °C; HCl salt: Mp 182—183 °C, lit,[14] mp 182—183 °C; ^{1}H NMR(CCl_4) δ=3.62 (3H, s, $OC\underline{H}_3$), 1.41 (2H, s, $N\underline{H}_2$), 1.25 (6H, s, $C\underline{H}_3$×2); IR (CCl_4) 3396 (ν_{NH}), 1730 ($\nu_{C=O}$), 1192 (ν_{CO}), 1142 (ν_{CO}).

Methyl 2-Aminobutanoate (5): Bp 68—70 °C; HCl salt: mp 149—150 °C, lit,[15] mp 150—151 °C; ^{1}H NMR (CCl_4) δ=3.60 (3H, s, $OC\underline{H}_3$), 3.23 (1H, t, J=7.0 Hz, C$\underline{H}$), 1.92—1.23 (2H, m, $C\underline{H}_2$), 1.30 (2H, s, $N\underline{H}_2$), 0.92 (3H, t, J=7.0 Hz, $C\underline{H}_3$); IR (CCl_4) 3404 (ν_{NH}), 1738 ($\nu_{C=O}$), 1174 (ν_{CO}), 1140 (ν_{CO}).

References

1) A. P. G. Kieboom and V. van Rantwijk, "Hydrogenation and Hydrogenolysis in Synthetic Organic Chemistry," Delft University Press, Delft (1977), p. 102.

2) H. Musso, "IUPAC Current Trends in Organic Synthesis," ed by H. Nozaki, Pergamon Press, Oxford and New York (1983), p. 371.

3) K. Isogai, J. Sakai, and K. Yamauchi, *Nippon Kagaku Kaishi*, **1986**, 214.

4) C. Groger, H. Musso, and I. Roβnagel, *Chem. Ber.*, **113**, 3261 (1980).

5) S. Mitsui, M. Fujimoto, Y. Nagahisa, and T. Sukegawa, *Chem. Ind. (London)*, **1969**, 241.

6) K. Isogai and K. Kitahara, *Nippon Kagaku Kaishi*, **1978**, 280.

7) K. Isogai and S. Hirabayashi, *Bull. Chem. Soc. Jpn.*, **52**, 3757 (1979).

8) K. Isogai, N. Nishizawa, T. Saito, and J. Sakai, *Bull. Chem. Soc. Jpn.*, **56**, 1555 (1983).

9) A. L. Schultz, *J. Org. Chem.*, **36**, 383 (1971).

10) C. H. DePuy, L. G. Schnack, and J. W. Hausser, *J. Am. Chem. Soc.* **88**, 3343 (1966).

11) S. J. Cristol, R. M. Seqeira, and C. H. DePuy, *J. Am. Chem. Soc.*, **87**, 4007 (1965).

12) M. J. O'Donnell. W. A. Bruder, T. M. Eckrich, D. F Shullenberger, and G, S. Staten, *Synthesis*, **1984**, 127.

13) D. Lim and O. Wichterle, *J. Polymer Sci.*, **29**, 579 (1958).

14) S.M. McElvain and E. H. Pryde, *J. Am. Chem. Soc.*, **71**, 326 (1949).

15) R. L. Smith and W. J. Polglase, *J. Biol. Chem.*, **180**, 1209 (1949).