Asymmetric Hydrogenation with Modified Raney Nickel. II. Studies on Modified Hydrogenation Catalyst. III

By Yoshiharu IZUMI, Masami IMAIDA, Hideaki FUKAWA and Shiro AKABORI

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In the previous paper[1], it was reported that R-Ni catalyst treated with L-Glu solution had asymmetric activity on the hydrogenation of some carbonyl compounds to alcohols, and that the activity was much influenced by pH and temperature of Glu solution.

In the present work, asymmetric activity of R-Ni catalyst treated with other sorts of amino acids, that is, *N*-substituted amino acids, hydroxy acids, and L-Glu dissolved in acetate buffer was studied in order to elucidate the mechanism of these asymmetric hydrogenations.

The asymmetric activity of catalyst modified with various amino acids $RCH(NH_2)COOH$ was tested in order to know the effect of substituent (R) on the asymmetric activity of a catalyst. In order to find out the role of the amino residue on the asymmetric activity of a catalyst modified with amino acid, *N*-substituted L-Asp and L-Glu derivatives were used as modifying reagents of the R-Ni catalyst. Since homocysteinic acid is structually analogous to Glu, the asymmetric activity of a catalyst modified with this amino acid was studied for the purpose of elucidating the effect of the structure of a molecule.

In order to elucidate the effect of the carbonyl group on the asymmetric activity of a catalyst modified with Glu, the modification was carried out in the presence of acetic acid. Because, if the asymmetric activity of the catalyst modified with Glu depends on the adsorption of the carbonyl group of Glu, some influence will occur in the presence of the carboxyl group of other acids.

The hydroxy acids were used as a homologue of amino acid used as modifying reagents. Experiments were carried out for the elucidation of the relationship between the absolute configuration of the modifying reagent and that of the hydrogenation product.

Result

In the case of Glu[1], the pH of the modifying solution influenced the asymmetric activity of the catalyst and the great asymmetric activity of the catalyst was obtained near the lower limit of the pH jump of neutralization curve of Glu. The neutralization curve of acidic substances, *N*-substituted L-Asp and L-Glu, D-tartaric acid, L-malic acid et al., were measured with sodium hydroxide solution. The lower and the upper limits of the pH jump of the neutralization curve of these substances

1) H. Fukawa, Y. Izumi, S. Komatsu and S. Akabori, This Bulletin, 35, 1703 (1962); Y. Izumi, M. Imaida, H. Fukawa and S. Akabori, ibid., 36, 21 (1963).

are shown in Table I. Thus the R-Ni catalyst was modified near the neutralization point of each substance and its asymmetric activity was tested.

Treatment with Several Amino Acids.—One and a half unit* of the R-Ni catalyst was treated with solutions of several amino acids as shown in Table II for 1.5 hr.

The asymmetric activity of the catalyst was tested in the hydrogenation of 17.0 g. of methyl acetoacetate to methyl 2-hydroxybutyrate at 60°C. The relationship between the asymmetric activity of the catalyst and modifying temperature is shown in Fig. 1.

From these results, amino acids could be divided into the following two groups.

The catalyst treated with L-Ala, L-Ser, L-Cystine, L-Thr and L-Pro at 0°C produced predominantly methyl D-2-hydroxybutyrate and the L-form contents of the reduced products increased according to the increase of the temperature of treatment. These amino acids

TABLE I. NEUTRAL POINT OF MODIFYING REAGENT

Modifying reagent	pH jump		
	Lower limit		Upper limit
N-Cyanoethyl-L-Asp.	First step	4.5	5.5
	Second step	9.0	11.0
N-Cyanoethyl-L-Glu.	First step	5.0	6.5
	Second step	9.0	11.0
N,*N*-Dimethyl-L-Glu.	5.5		8.0
N-Acetyl-L-Glu.	6.0		10.5
N-Benzyl-L-Glu.	6.0		10.0
D-Tartaric acid	5.0		11.0
L-Malic acid	6.0		11.0
L-Homocysteinic acid	4.0		8.0

TABLE II. MODIFYING SOLUTION OF AMINO ACID

No.	Amino acid (g.)	Water ml.	pH observed
1	L-Alanine (2.7)	225	7.20
2	L-Serine (3.0)	225	6.60
3	L-Threonine (4.5)	225	6.12
4	L-Proline (3.5)	225	8.10
5	L-Cystine (0.1)	400	7.80
6	L-Tryptophan (6.0)	300	7.00
7	L-Phenylalanine (4.5)	225	7.05
8	L-Aspartic acid (4.5)	225	4.65
9	L-Valine (4.5)	225	6.00
10	L-Isoleucine (4.5)	225	6.30
11	L-Leucine (4.5)	225	7.32
12	L-Methionine (4.5)	225	6.90
13	L-Arginine (5.0)	225	10.80
14	L-Tyrosine (1.0)	225	7.02
15	L-Lysine·HCl (5.0)	225	7.02
16	L-Histidine·HCl (6.0)	225	4.20

* One unit of R-Ni was prepared from 1.0 g. R-Ni alloy by the method described in the previous paper[1].

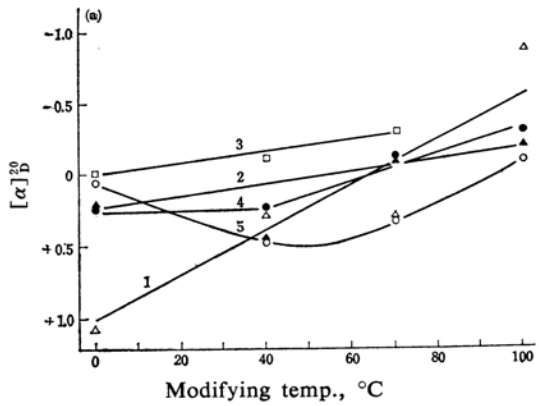

Fig. 1 (a).

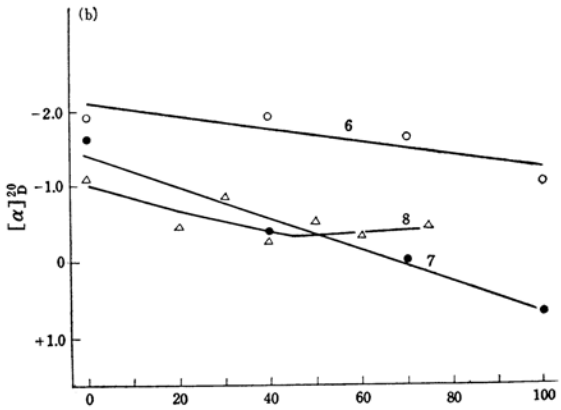

Fig. 1 (b).

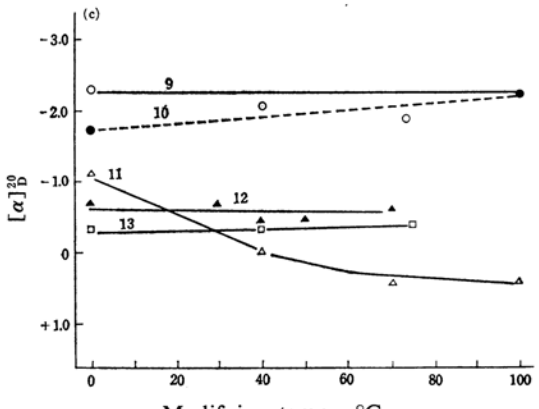

Fig. 1 (c).

1. L-Alanine
2. L-Serine
3. L-Threonine
4. L-Proline
5. L-Cystine
6. L-Tryptophan
7. L-Phenylalanine
8. L-Aspartic acid
9. L-Valine
10. L-Isoleucine
11. L-Leucine
12. L-Methionine
13. L-Arginine
14. L-Tyrosine
15. L-Lysine·HCl
16. L-Histidine·HCl

belong to the amino acids of which the L-form has a sweet taste. Modification by amino acids other than the amino acids mentioned above resulted in giving the catalyst which produces predominantly methyl L-2-hydroxybutyrate at 0°C. Some of the catalysts modified at higher temperature increased the content of the D-form of reduced products as in the case of modification by L-Glu.

L-Met and L-Cys are probably desulfurized by R-Ni during the treatment, so it was omitted from consideration.

The asymemtric activity of the catalyst modified by L-Tyr, L-Lys and L-His are shown in Table III. When the hydrochlorides of L-Lys and L-His were used as the modifying reagents at higher temperature, the chloride anion brought about a remarkable depression of hydrogenation activity of the catalyst; therefore, the asymmetric activity of the catalyst could not be measured.

Table III. Effect of the modifying temperature

Modifying reagent	Modifying temp., °C	$[\alpha]_D^{20}$ of Me 2-hydroxybutyrate
L-Tyr	100	−0.50
L-Lys (HCl)	0	−1.45
L-Lys (HCl)	40	−1.42
L-His (HCl)	0	−0.04

(Catalyst modified with amino acid)

Because of the lower solubility of L-Tyr, the effect of temperature on the asymmetric activity could not be measured at a lower modifying temperature.

***N*-Substituted L-Asp and L-Glu Derivatives.**— One and a half unit of the R-Ni catalysts were modified in the neighborhood of the pH jumps of the modifying reagents under the conditions shown in Table IV and the results are shown in this table.

Table IV. Modifying condition with acidic modifying reagent

R-Ni (unit)	Modifying reagent, g.	Conditions of treatment				Substrate Me acetoacetate g.	$[\alpha]_D^{20}$ of Me 2-hydroxybutyrate
		pH	Solvent ml.	Temp. °C	Time hr.		
1.5	*N*-Cyanoethyl-L-Asp. (2.0)	3.91	100	0	1.5	17	−0.14
1.5	*N*-Cyanoethyl-L-Asp. (2.0)	4.60	100	0	1.5	17	−0.08
1.5	*N*-Cyanoethyl-L-Asp. (2.0)	6.80	100	0	1.5	17	0
1.5	*N*-Cyanoethyl-L-Asp. (2.0)	8.04	100	0	1.5	17	−0.16
1.5	*N*-Cyanoethyl-L-Asp. (2.0)	8.48	100	0	1.5	17	0
1.5	*N*-Cyanoethyl-L-Asp. (2.0)	10.80	100	0	1.5	17	+0.03
1.5	*N*-Cyanoethyl-L-Asp. (2.0)	8.46	100	100	1.5	17	0
1.5	*N*-Cyanoethyl-L-Glu. (2.0)	4.70	100	0	1.5	17	−0.10
1.5	*N*-Cyanoethyl-L-Glu. (2.0)	6.44	100	0	1.5	17	−0.16
1.5	*N*-Cyanoethyl-L-Glu. (2.0)	8.08	100	0	1.5	17	−0.20
1.5	*N*-Cyanoethyl-L-Glu. (2.0)	9.19	100	0	1.5	17	−0.26
1.5	*N*-Cyanoethyl-L-Glu. (2.0)	9.17	100	100	1.5	17	−0.18
1.5	*N*,*N*-Dimethyl-L-Glu. (2.0)	5.01	100	0	1.5	17	−0.75
1.5	*N*,*N*-Dimethyl-L-Glu. (2.0)	5.59	100	0	1.5	17	−0.72
1.5	*N*,*N*-Dimethyl-L-Glu. (2.0)	5.02	100	100	1.5	17	−0.40
1.5	*N*-Benzoyl-L-Glu. (2.0)	5.60	100	0	1.5	17	+0.15
1.5	*N*-Benzoyl-L-Glu. (2.0)	4.90	100	100	1.5	17	−0.33
1.5	*N*-Benzoyl-L-Glu. (2.0)	5.55	100	100	1.5	17	−0.67
1.5	L-Homocysteinic A. (2.0)	7.10	100	0	1.5	17	−0.15
1.5	L-Homocysteinic A. (2.0)	7.10	100	100	1.5	17	+0.15
1.5	L-Homocysteinic A. (2.0)	3.90	100	0	1.5	17	−0.23
1.5	L-Homocysteinic A. (2.0)	3.90	100	100	1.5	17	+0.19
1.5	L-Malic A. (2.0)	4.08	100	0	1.5	17	+1.85
1.5	L-Malic A. (2.0)	5.22	100	0	1.5	17	+2.35
1.5	L-Malic A. (2.0)	5.52	100	0	1.5	17	+2.20
1.5	L-Malic A. (2.0)	5.70	100	0	1.5	17	+1.95
1.5	L-Malic A. (2.0)	6.30	100	0	1.5	17	+1.68
1.5	L-Malic A. (2.0)	5.39	100	100	1.5	17	+4.57
1.5	L-Malic A. (2.0)	5.61	100	100	1.5	17	+4.70

TABLE V. EFFECT OF ACETIC ACID

No.	R-Ni (unit)	Conditions of modification: 5 M Acetate buffer (pH 5.0) ml.	Temp. °C	2% L-Glu (pH 5.0)	Time hr.	Substrate (Me acetoacetate), g.	$[\alpha]_D^{20}$ of Me 2-hydroxybutyrate
1	1.5	none	0	225	1.5	17	−3.51
2	1.5	5*	0	25	1.5	17	−1.99
3	1.5	5**	0	225	1.5	17	−2.50
4	1.5	50**	0	225	1.5	17	−2.62

* Treated with acetate buffer and then modified with Glu solution.
** Treated with mixture of acetate buffer and Glu solution.

TABLE VI. MODIFYING CONDITION WITH HYDROXY ACID

No.	R-Ni (unit)	Modifying reagents g.	Conditions of treatment: pH	Water ml.[3]	Temp. °C	Time hr.	Substrate (Me Acetoacetate. g.
1	1.5	D-Tartaric A. (2.0)	**2.1～12.3**[1]	100～130	0	1.5	17.0
2	1.5	D-Tartaric A. (2.0)	**4.4～5.9**[1]	130	100	1.5	17.0
3	1.5	D-Tartaric A. (2.0)	5.1～5.2	125	**0～100**[1]	1.5	17.0
4	1.5	D-Tartaric A. (2.0)	5.1～5.2	125	100	**0.1～2.5**[1]	17.0
5	1.5	D-Tartaric A. (**0.015～20.0**)[1]	5.1～5.2	100～360	100	1.5	17.0
6	1.5	L-Malic A. (2.0)	**4.1～6.3**[1]	114～129	0	1.5	17.0
7	1.5	L-Malic A. (2.0)	**5.4～5.6**[1]	127	100	1.5	17.0
8	1.5	Diethyl-L-tartarate (2.0)	—[2]	100[2]	—[4]	1.5	17.0

1) Effect of these conditions is discussed in the other.
2) Ethanol, pH was not measured.
3) pH was adjusted with 1 N NaOH exactly, so total volume of the modifying solution varied with the amount of the modifying reagent.
4) R-Ni was treated under reflux.

These results show that asymmetric activity of the catalyst has no close correlation with basicity of the nitrogen of the modifying reagent, but is much influenced by the steric effect of the substituent.

Homocysteinic Acid $HOOCCH_2CH_2CH(NH_2)\cdot SO_3H$.—The conditions for the preparation of the catalyst and the results are shown in Table IV. Asymmetric activity of this catalyst is much less than that prepared with Glu. But other characteristics of these catalysts resemble each other.

Effect of Acetic Acid on the Modification with Glu.—When the catalyst was prepared by the treatment with Glu in acetate buffer, the asymmetric activity of the catalyst was less, as compared with that treated without acetic acid, as shown in Table V.

Hydroxy-carboxylic Acid.—The modification of the catalsyt with hydroxy carboxylic acid was carried out with the solution shown in Table VI.

1) D-Tartaric Acid. — *Effect of pH (Table VI-No. 1, 2).*—The relation between the pH of the modifying solution and the asymmetric activity of catalyst at 0°C is shown by curve 1 in Fig. 2 and the neutral point is shown in Table I.

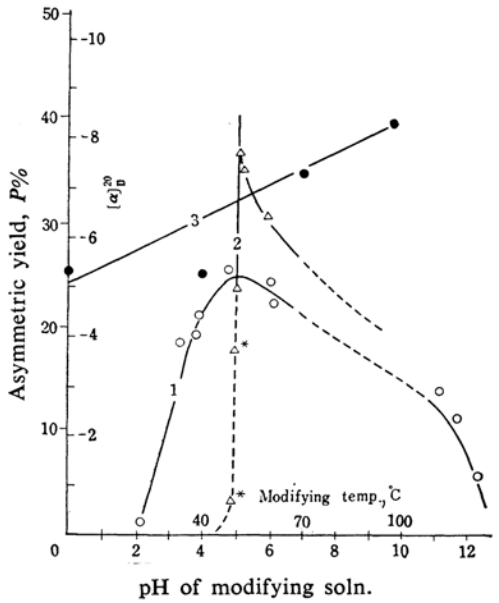

Fig. 2. Effect of modifying pH and temperature.
1 -○- Effect of modifying pH at 0°C
2 -△- Effect of modifying pH at 100°C
3 -●- Effect of modifying temperature
* Calculated value

When the catalyst was treated at 100°C below pH 5.0, the catalyst distinctly decreased its hydrogenating and asymmetric activities as can be seen from curve 2 in Fig. 2.

Effect of Temperature (Table VI-No. 3).—When the temperature of treatment rose, the asymmetric activity increased as shown by curve 3 in Fig. 2. The pH of the modifying solution moved towards alkaline after treatment at higher temperature.

Effect of Temperature (Table VI-No. 4).—The asymmetric activity of catalysts at various immersion time are presented in Fig. 3. The activity became almost constant in 30 min. and one and a half hours is sufficient to gain the constant asymmetric activity.

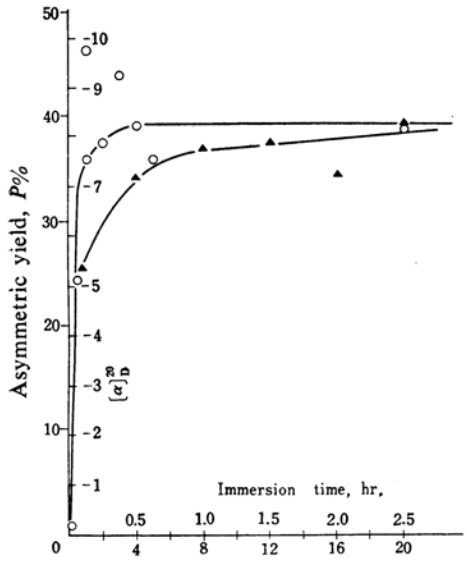

Fig. 3. Effect of concentration of modifying solution and immersion time of catalyst.
-○- Effect of amount of tartaric acid
-▲- Effect of immersion time

Effect of the Concentration of Modifying Solution (Table VI-No. 5).—Effect of the concentration of modifying solution on the asymmetric activity of a catalyst was tested by the treatment with the solution which contained various amounts of tartaric acid. The results are shown in Fig. 3. The constant aymmetric activity was gained when the catalyst was treated with solutions of the concentration above 1.0 per cent. The lowest limit of the concentration is much higher than that of Glu, because tartaric acid has less buffer action than Glu.

2) L-Malic Acid (Table VI-No. 6, 7). — In the case of L-malic acid the greatest asymmetric activity was obtained on the treatment with the solution near its pH jump, as shown in Table I. The asymmetric activity of the catalyst treated at 100°C was greater than that treated at 0°C. The asymmetric activity of this catalyst was about a half of that of the catalyst treated by tartaric acid under the same condition as shown in Table IV.

Discussion

From the results of the three reports of this series[1], it is concluded that asymmetric catalysts are obtained by contacting R-Ni with the solution containing asymmetric compounds.

The modifying reagents used in the experiments must have the substituents of high affinity to nickel, such as $-NH_2$, $-COOH$ and $-OH$ groups at the asymmetric center. With amino acid $RCH(NH_2)COOH$ which have residues (R) possessing higher affinity to nickel gave catalysts of higher asymmetric activity.

Absolute configuration of methyl 2-hydroxybutyrate was affected by the structure of amino acid which was used to modify the R-Ni. The catalysts modified at 0°C with the L-amino acids of small molecular size (sweet taste) predominantly produce the D-form of hydrogenation products, while with L-amino acids of large molecular size (no sweet taste) predominantly produce L-form products.

The *N*-substituted amino acid, acyl, dimethyl or cyanoethyl derivatives, produce much less asymmetric activity of the catalyst. From this evidence, $-NH_2$ residue might greatly participate in making the asymmetric center of the catalyst. From the results described above it could be concluded that the lone pair of nitrogen atom in amino residue must touch on the surface of the catalyst to make asymmetric center.

The treatment with malic acid and tartaric acid cause the powerful asymmetric activity of the catalyst, but the treatment with diethyl tartrate does not. The catalyst treated with Glu dissolved in acetate buffer has much less asymmetric activity than that treated with aqueous Glu solution. These facts show that, with amino or hydroxy acid, the carboxyl group is important to make the asymmetric center on R-Ni. These facts also agree with the results reported by Welch[2] et al. who describe that ester is slightly adsorbed and two different fatty acids are competitively adsorbed by the R-Ni catalyst.

Asp and malic acid resemble each other in the structure, but the asymmetric activity of a catalyst treated with Asp is considerably smaller than that of a catalyst treated with

2) C. M. Welch, H. A. Smith and J. B. Cole, *J. Phys. Chem.*, 65, 705 (1961).

malic acid. The same relation is found in homocysteinic acid and Glu. The asymmetric activity of a catalyst treated with tartaric acid is much higher than that of a catalyst treated with malic acid. This result corresponds to that tartaric acid and malic acid are 170 and 135 in molecular weight and have two and one active center, respectively. So far as the Stuart's model is used for consideration, it is assumed that these differences depend on whether the molecules on the modifying reagents can attach to the surface of R-Ni without any steric hindrance or not.

Absolute configuration of D-tartaric acid opposed to that of L-malic acid, and the optical rotation of methyl 2-hydroxybutyrate which was produced by the hydrogenation of methyl acetoacetate in the presence of the catalyst treated with these acids, opposed each other. L-Asp and L-malic acid have the same absolute configuration, but the asymmetric activity of a catalyst treated with these reagents have opposit asymmetric activity. From these results, it seems that there are some differences of structure between the asymmetric center of catalysts produced with amino acids and hydroxy acids.

Moreover, the fact that L-Pro produces slightly asymmetric activity is a clear evidence that the asymmetric center of hydrogenation can not be produced by the two-points attachment with carboxyl and amino groups. If this center is produced by the two points-attachment the pyrrolidin ring must stand up outside of the R-Ni surface and a strong steric effect must be produced.

It is concluded that the following two considerations are required for producing the asymmetric activity of R-Ni.

1) R-Ni must adsorb the asymmetric compounds which contain three substituents with affinity to Ni.

2) In order to obtain higher asymmetric activity of the catalyst, it is essential that the molecules of modifying reagents are adsorbed on the R-Ni easily and tightly.

Experimental

Preparation of the catalyst, hydrogenation of methyl acetoacetate and measurement of asymmetric yield were carried out in the same manner as described in the previous paper[1].

Modification of the Catalyst.—The R-Ni catalyst was modified under the conditions shown in Tables IV and VI. The procedure is quite similar to the modification with Glu which was described in the previous paper. The aqueous solution which contained acidic modifying reagent was neutralized with 1 N sodium hydroxide solution and adjusted to a suitable pH.

Effect of Acetic Acid. — *Experiment No. 2 in Table V.* — One and a half unit of R-Ni catalyst treated with 5 M acetate buffer (pH 5.0) at 0°C for 10 min., washed with 50 ml. of cold water, then was modified with 25 ml. of 2% Glu at 0°C for 1.5 hr. as usual method.

Experiment No. 3 and 4 in Table V.—One and a half unit of R-Ni catalyst was modified with the solution containing 225 ml. of 2% Glu which was adjusted to pH 5.02 and 5 ml. (or 50 ml.) of 5 M acetate buffer (pH 5.0) at 0°C for 1.5 hr.

Summary

1) The asymmetric R-Ni catalysts were prepared by the treatment of R-Ni with various asymmetric compounds, and the asymmetric activity of a catalyst was measured by the hydrogenation of methyl acetoacetate

2) Optical rotatory direction and power of the reduced product was affected both by the configuration and molecular size of amino acid which was used as modifying reagent.

3) The asymmetric activity of catalysts treated with *N*-substituted amino acids, *N*-acyl, *N*-dimethyl and *N*-cyanoethyl derivatives of Glu and Asp, were much less than the activity of the catalyst treated with the corresponding amino acids.

4) The asymmetric activity of the catalyst treated with D-tartaric acid and L-malic acid was tested at various conditions. The asymmetric yield in the hydrogenation of methyl acetoacetate in the presence of the catalyst treated with D-tartaric acid solution of pH 5.1 ~5.2 at 100°C was about 45 percent.

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Division of Organic Chemistry
Institute for Protein Research
Osaka University
Kita-ku, Osaka