Neutron and γ-Irradiation of Propionamide

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When molecules containing nitrogen atoms are irradiated with neutron, the nuclear transformation

$$^{14}N + n \rightarrow (^{15}N)^* \rightarrow {}^{14}C + p$$

takes place. A carbon-14 atom thus produced immediately ruptures the bond which holds it due to its tremendous recoil energy and becomes a hot atom. Therefore, an unusual reaction is expected to occur as the hot atom loses its energy by collision. As an example of neutron irradiation of nitrogenous organic compound, ammonium nitrate was first studied with a view of the production of carbon-14 activity by Ruben and Kamen(1) in 1940. Recently, several researchers have attempted the neutron irradiation of many compounds(2). But these results were not completely accounted for either by the simple random substitution of carbon atom or, of course, by ordinary thermal reaction.

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1) S. Ruben and M. D. Kamen, *Phys. Rev.*, 57, 549 (1940).

2) R. C. Extermann, "Radioisotopes in Scientific Research", Vol. II, Pergamon Press, London (1958), p. 114.

In order to examine the mechanism of hot atom reaction in detail, the present authors carried out the neutron irradiation of propionamide and found that the methylation of the amide was the main results and the authors determined the activity distributions in the products: ^{14}C-propionamide, ^{14}C-butyramide, ^{14}C-isobutyramide, ^{14}C-ethyl methyl ketone. Methyl radicals produced by γ-irradiation are less energetic than the hot atoms produced from the nuclear transformation. In order to compare the reactivity of the carbon-14 hot atoms with those of methyl radicals from carbon-carbon bond fissions by γ-ray irradiation, the γ-ray irradiation of propionamide-(carbonyl-^{14}C) was studied also in the present work and the yields of butyramide and isobutyramide were determined by the isotope dilution method.

Moreover, the reaction of propionic acid with thermal methyl radicals produced by the decomposition of acetyl peroxide was studied and the abnormality in the distribution of products in the above cases is discussed in comparison with the result of the thermal reaction.

Experimental

Neutron Irradiation.—*Irradiation of Sample.*—Propionamide was synthesized from propionic acid and ammonium carbonate by Coleman-Alvarado's method(3) and recrystallized from methanol-ether solution. The butyramide and isobutyramide used as carriers were synthesized by the same method as propionamide. Commercial ethyl methyl ketone was purified by fractionation with a Podbielniak high temperature distillation apparatus (60-plates heli-grid packing column). Fifteen grams of the propionamide were covered with a polyethylene sheet and then packed in a polyethylene capsule. The assembled mass was iraadiated in the J. R. R.-1 reactor at an approximate flux of 10^{11} neutron/cm^2/sec. for about 120 hr. After irradiation, about a month was allowed for the decay of short-lived species in the capsule. As soon as it was opened, the irradiated sample was separated into several portions for the subsequent experiments.

Separation of Products.—To separate butyramide and isobutyramide a carrier was added to the irradiated sample. In the case of propionamide, some more non-active carrier was added. The mixture was hydrolyzed by refluxing for 2 hr. with 50% hydrochloric acid and the resulting substance was purified by distillation and by a Podbielniak gas chromatography on a 1/4″×4ft. column containing fire brick celite (30~80 mesh): 50% D. C. 710 silicone plus 10% stearic acid constituted the liquid phase. The column temperature was kept at 100°C and helium was used as the carrier gas.

Separation of Ethyl Methyl Ketone.—Ethyl methyl ketone was separated as 2,4-dinitrophenyl hydrazone by addition of 2,4-dinitrophenylhydrazine and this was recrystallized from ethanol several times to give a constant specific activity.

TABLE I. THE QUANTITIES OF IRRADIATED SAMPLE AND CARRIERS

Separated sample	Irradiated sample, g.	Carrier, g.
Propionic acid	4.133	—
Butyric acid	3.465	4.809
Isobutyric acid	3.465	4.581
Ethyl methyl ketone	0.243	1.193

γ-Irradiation.—*Irradiation of Sample.*—About 5 g. of propionic acid purified with the distillation apparatus was added to sodium propionate (carbonyl-^{14}C) (0.1 mg., 0.1 mc./mg.). Propionyl chloride-(carbonyl-^{14}C) was synthesized from the mixture and benzoyl chloride by the method that is cited in the literature(4). The distillate up to 81°C was dissolved in benzene and converted to propionamide-(carbonyl-^{14}C) with ammonia. It was recrystallized from methanol-ether several times to give a constant specific activity of 4.7×10^2 μc./mol. Three grams of the propionamide-(carbonyl-^{14}C) were irradiated by the 10000-curie ^{60}Co γ-source(4) with a dose rate of 1.2×10^5 r./hr. at room temperature. The dose rate was determined by both cerous-ceric(6) and ferric-ferrous(7) dosimeter. The absorbed dose was 2×10^8 r.

After irradiation the sample was separated into several portions for the subsequent experiments.

Separation of Products.—In this case, propionamide was added as a hold back carrier, also. Acids were separated by the same procedure as that described above. The acids were converted again to amide by benzoyl chloride and ammonia and then were recrystallized.

TABLE II. THE QUANTITIES OF IRRADIATED SAMPLE AND CARRIERS

Separated sample	Irradiated sample, g.	Carrier g.	Hold back carrier, g.
Butyric acid	1.00	1.50	2.00
Isobutyric acid	1.00	1.50	2.00

3. Decomposition of Acetyl Peroxide in Propionic Acid-(Carboxyl-^{14}C). — *Preparation and Purity of Acetyl Peroxide.*—Acetyl peroxide was synthesized by the Gambarjan method(8) modified by Kharasch(9).

Its purity was 99.86%.

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3) G. H. Coleman and A. M. Alvarado, "Organic Syntheses", Coll. Vol. I, (1948), p. 3.

4) N. D. Cheronis, "Technique of Organic Chemistry", Vol. VI, "Micro and Semimicro Method", Interscience Publishers, Inc., New York (1954), p. 284.

5) A. Danno et al., Abstract of the 7th Hot Laboratories and Equipment Conference, Cleveland (1959), p. 349~360.

6) For example, T. Rigg, G. Stein and J. Weiss, *Proc. Roy. Soc.*, **A211**, 375 (1952).

7) G. R. A. Johnson and J. Weiss, ibid., **A240**, 189 (1952).

8) S. Gambarjan, *Ber.*, **42**, 4010 (1909).

9) M. S. Kharasch, H. C. Mckay and W. H. Urry, *J. Org. Chem.*, **10**, 394 (1945).

Propionic Acid-(Carboxyl-^{14}C).—Non-active propionic acid which was purified by the Podbielniak high temperature distillation apparatus was added to the sodium propionate-(carboxyl-^{14}C) (0.1 mc./mg.).

The mixture was purified by several distillations in the distillation apparatus. The specific activity of the purified propionic acid-(carboxyl-^{14}C) was 4.25 mc./mol.

Decomposition of Acetyl Peroxide.—Acetyl peroxide (507.8 mg.) was dissolved in 4.00 ml. of propionic acid-(carboxyl-^{14}C). The mixture was heated at 95∼100°C for five hours.

Separation of Acids.—Acids were separated and purified by the same procedure as in the case of γ-irradiation.

TABLE III. THE QUANTITIES OF SOLUTION AND CARRIERS

Separated sample	Reaction mixture, ml.	Carrier ml.	Hold back carrier, ml.
Isobutyric acid	1.00	2.00	2.00
Butyric acid	1.00	2.00	2.00

Oxidation and Counting.—The purified compounds were converted to carbon dioxide by the Van Slyke-Folch oxidation method[10].

The resulting carbon dioxide was absorbed by 0.74 N sodium hydroxide solution and then precipitated as barium carbonate by the addition of barium chloride-ammonium chloride solution. The specific activity of the barium carbonate was measured at infinite thickness by a Tracerlab T. G. C-14 counter.

Result and Discussion

The obtained results about the neutron irradiation of propionamide are shown on Table IV. The approximate relative ratio of the yields of ethyl methyl ketone, butyric acid, isobutyric acid, propionic acid were 1:2:3:4. ^{14}C-Propionamide would be produced by the replacement of a carbon atom in the parent molecule with the recoiling carbon-14.

$$\mathrm{CH_3CH_2CONH_2} \xrightarrow{^{14}\mathrm{N\,(n,\,p)}\,^{14}\mathrm{C}} \text{recoil } ^{14}\mathrm{C} + \text{molecular fragments} \qquad (1)$$

$$\text{recoil } ^{14}\mathrm{C} + \mathrm{CH_3CH_2CONH_2} \longrightarrow \begin{array}{l} ^{14}\mathrm{CH_3CH_2CONH_2} \\ \mathrm{CH_3{}^{14}CH_2CONH_2} \\ \mathrm{CH_3CH_2{}^{14}CONH_2} \end{array} + \text{knockon-}^{12}\mathrm{C} + \text{etc.} \qquad (2)$$

Ethyl methyl ketone was produced by a "knockon" reaction by ^{14}C at nitrogen in the parent compound. Butyramide and isobutyramide were formed by the replacement of hydrogen in propionamide with ^{14}C-radicals, respectively.

$$(^{14}\mathrm{CH_3}\cdot)^* \text{ or } (^{14}\mathrm{CH_2}:)^* + \mathrm{CH_3CH_2CONH_2} \longrightarrow {}^{14}\text{C-butyramide or } {}^{14}\text{C-isobutyramide} + \text{etc.} \qquad (3)$$

It is known that in ordinary free radical reactions, the hydrogen attached to a secondary carbon atom is more reactive with a free radical than that attached to a primary carbon atom. If butyramide and isobutyramide were formed by the thermal reaction of free methyl or methylene radical, the yield of isobutyramide which would be produced by the substitution of the hydrogen atom attached on the secondary carbon of propionamide would be much larger than that of butyramide. However, the ratio of the yields of butyr- and isobutyramide in the present study was about 3:2 as is shown in Table IV. The value agrees with the ratio of the number of hydrogen atoms available for substitution in the propionamide to give butyr- or isobutyramide. Accordingly, another mechanism should be considered instead of the ordinary free radical mechanism. Here the present authors propose the following mechanism:

(1) ^{14}C-Propionamide is produced by a "knockon" reaction of the carbon in the compound by the carbon-14 having high kinetic energy. (Eq. 2). (2) Most of the recoil carbon-14 are cooled by collisions with atoms or molecules to some extent so that its energy would be in the order of 25∼50 eV.[11] However the recoil carbon-14 is extremely active and reacts with its surroundings, and its predominant tendency will be to gain hydrogens as follows.

$$\text{recoil carbon-14} + \text{organic matrix} \longrightarrow {}^{14}\mathrm{CH_3}\cdot,\ {}^{14}\mathrm{CH_2}:,\ {}^{14}\mathrm{CH_3}^{+},\ \text{etc.} \qquad (4)$$

The energy of these radicals will be so high that, at random, substitution reaction will occur. Assuming the above mechanism, the distribution of activity in butyric and isobutyric acid would be 3:2.

γ-Irradiation.—When the organic compounds are irradiated by γ-rays, the C-H, and C-C bonds are broken to yield $\mathrm{CH_3}$ and other radicals. To compare the reactivity of the radicals produced by γ-irradiation with that of ^{14}C-hot atom, the ^{60}Co γ-ray irradiation of propionamide-(carbonyl-^{14}C) was performed. Methyl radical, ethyl radical, carbon monoxide and so on are formed from propionamide by γ-rays irradiation. Methyl radical attacks the propionamide to produce butyramide or isobutyramide. The ratio of the yield of butyramide- and isobutyramide was determined by the

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[10] D. D. Van Slyke and H. Folch, *J. Biol. Chem.*, **136**, 509 (1940).

[11] A. P. Wolf, C. S. Redvanly and C. Anderson, *J. Am. Chem. Soc.*, **79**, 3717 (1959).

TABLE IV. THE NEUTRON IRRADIATION OF PROPIONAMIDE

Product	Activity, μc. 1.	Activity, μc. 2.	Average	% to the total activity	Relative ratio
Propionamide	1.40	1.30	1.35	3.3	4.2
Butyramide	0.86	0.90	0.88	2.1	2.7
Isobutyramide	0.69	0.71	0.70	1.7	2.1
Ethyl methyl ketone	0.31	0.33	0.32	0.8	1.0
Total activity	42.0	40.0	41.0		

TABLE V. γ-IRRADIATION OF PROPIONAMIDE (CARBONYL-^{14}C)

Product	Activity, $\times 10^{-1}$ μc. 1.	Activity, $\times 10^{-1}$ μc. 2.	Average, $\times 10^{-1}$ μc.	Relative ratio	G-Value
Butyramide	2.49	2.68	2.59	3.1	0.83
Isobutyramide	1.65	1.61	1.63	2.0	0.53

isotope dilution method using propionamide-(carbonyl-^{14}C.).

As it is shown in Table V, the ratio of the yield of butyric acid to that of isobutyric acid from the corresponding amides was 3:2. This ratio shows a good agreement with that in the case of the neutron irradiation.

These results can not be explained by thermal free radical reactions, but by the following mechanism: Propionamide decomposes to methyl and other radicals by the action of γ-rays as indicated by Eq. 5.

$$CH_3CH_2CONH_2 \xrightarrow{\gamma\text{-rays}} CH_3\cdot,\ CH_3CH_2\cdot,\ CONH_2\cdot,\ \text{etc.} \qquad (5)$$

The energy of methyl radicals will be so high that random substitutions will take place. Its energy, perhaps, is in the order of 5~10 eV.[12], so that the so-called "high energy reaction" should be considered to take place in this case and, by this mechanism, the present experimental results can be sufficiently explained.

Thermal Free Radical Reaction in Solution.—In order to compare such a high energy reaction as that indicated above with thermal free radical reaction, decomposition of acetyl peroxide in propionic acid-(carboxyl-^{14}C) was carried out.

Acetyl peroxide is decomposed in solution by heat as follows.

$$(CH_3COO)_2 \xrightarrow{\text{heat}} CH_3\cdot + CO_2\cdot + CH_3COO\cdot \qquad (6)$$

Most of the methyl radicals would carry out hydrogen abstraction reaction on the analogy of the reaction of acetyl peroxide with acetic acid[13].

However some of the methyl radicals formed combine with propionic acid-(carboxyl-^{14}C) to give butyric acid-(carboxyl-^{14}C) or isobutyric acid-(carboxyl-^{14}C). The isotope dilution method was applied to the determination of the ratio of butyric and isobutyric acid. The results are summarized in Table VI and the ratio of the yields of butyric and isobutyric acid is 1:2. The number of hydrogen atoms available for the substitution being taken into account, the result of the above ratio is that the hydrogen atom at the 2-position is three times more reactive with methyl radical compared with that at the 3-position, in the case of the substitution reaction of propionic acid. This result is quite different from those in the cases of neutron and γ-ray irradiation. The reaction of methyl radical from acetyl peroxide with propionic acid must be classified as a typical thermal free radical reaction in solution.

TABLE VI. THE DECOMPOSITION OF ACETYL PEROXIDE IN PROPIONIC ACID (CARBOXYL-^{14}C)

Product	Activity, $\times 10^{-1}$ μc.	Relative ratio
Butyric acid	2.31	1.0
Isobutyric acid	5.14	2.2

Summary

Two methylation reactions of propionamide by ^{14}C-hot atom, and of methyl radical from ^{60}Co γ-ray irradiation and methylation reaction of propionic acid by methyl radical from thermal decomposition of acetyl peroxide were carried out and the reactivities of these species were studied. The methyl radical produced by ^{60}Co γ-ray irradiation of propionamide gave the 3:2 mixture of butyr- and isobutyramide. This ratio agrees with the activity distribution of butyr- and isobutyramide in the neutron irradiation of propionamide. On the other hand the methyl radical produced by the

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[12] T. Watanabe, private communication.

[13] A. Fry, B. M. Tolbert and M. Calvin, *Trans. Faraday. Soc.*, **49**, 1444 (1953).

thermal decomposition of acetyl peroxide in propionic acid gave 1:2 mixture of butyric and isobutyric acid. From the above results the reactions in the neutron irradiation and in the γ-ray irradiation are considered to be high energy reactions, whereas the methylation reaction of acetyl peroxide in propionic acid is considered to be a free radical reaction.

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