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A NEW METHOD FOR THE PREPARATION OF CARBOXYL-LABELLED ALIPHATIC CARBOXYLIC ACIDS

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Abstract—The exchange reaction of carboxyl groups with labelled carbon dioxide has been investigated and shown to provide an excellent method for the preparation of labelled aliphatic carboxylic acids.

It is known[1-3] that an exchange reaction of carboxylate groups (Fig 1) occurs during the thermal decomposition of mixtures of aliphatic carboxylic acid

$$\text{R–}^{14}\text{COOM} \longleftrightarrow \text{R–COOM}$$
$$\text{R'COOM} \longleftrightarrow \text{R'–}^{14}\text{COOM}$$

Fig 1

salts. The rate of exchange depends chiefly on the cation applied in the order Li < Na < K[4]. Studies[5] of this exchange process led to the assumption of the mechanism shown in Fig 2

$$\text{R–CH}_2\text{–COOM} \longrightarrow \text{R–}\bar{\text{C}}\text{H}_2\text{M}^+ + \text{CO}_2$$
$$\text{R–CH}_2\text{–COOM} + \text{R–CH}_2\text{M}^+ \longrightarrow \text{R–}\underset{\text{COOM}}{\bar{\text{C}}}\text{HM}^+ + \text{R–CH}_3$$
$$\text{R–}\underset{\text{COOM}}{\bar{\text{C}}}\text{HM}^+ \underset{-{}^{14}\text{CO}_2}{\overset{+{}^{14}\text{CO}_2}{\rightleftharpoons}} \text{R–CH}\begin{matrix}{}^{14}\text{COOM}\\ \text{COOM}\end{matrix} \underset{+\text{CO}_2}{\overset{-\text{CO}_2}{\rightleftharpoons}} \text{R–}\underset{{}^{14}\text{COOM}}{\bar{\text{C}}}\text{HM}^+$$
$$\text{R–}\underset{{}^{14}\text{COOM}}{\bar{\text{C}}}\text{HM}^+ + \text{R–CH}_2\text{–COOM} \rightleftharpoons \text{R–CH}_2\text{–}^{14}\text{COOM} + \text{R–}\underset{\text{COOM}}{\bar{\text{C}}}\text{HM}^+$$

Fig 2

In this mechanism the postulated malonate-type intermediate of exchange is formed in the reaction of carbanions with carbon dioxide. Accordingly, we observed high radioactivity incorporation into the acids recovered when their potassium or sodium salts were heated in carbon-^{14}C dioxide atmosphere. This observation permitted the elaboration of a new method for the preparation of carboxylic-1-^{14}C acids. For the preparative application of the exchange occuring between the carboxylate groups and carbon-^{14}C dioxide (Fig 3) we determined the optimal conditions of the reaction in a number of salts. The experimental results are summarized in Table I.

$$\text{R–COOM} \underset{\text{CO}_2}{\overset{{}^{14}\text{CO}_2}{\rightleftharpoons}} \text{R–}^{14}\text{COOM}$$

Fig 3

As can be seen from the data in many cases the exchange is very fast and equilibrium distribution of ^{14}C between the carboxylate group and carbon dioxide can be reached with a few percent decomposition of the salt. This difference in the reaction rates of thermal transformations of salts allows conversion of an aliphatic acid to the carboxyl labelled species with very simple apparatus and requires only a short time compared to the methods used earlier.[6] Further advantage of the method is that the starting material is the corresponding non-radioactive carboxylic acid and that the residual carbon-^{14}C dioxide can be easily recovered from the reaction mixture.

In accordance with the mechanism presented in Fig 2, the exchange reaction cannot be applied for labelling carboxylic acids with no α-hydrogen content, nor can it be used for acid molecules containing substituents reactive to α-carbonions or carboxylic acid salts (–NH_2, OH, halogen, etc). According to the above mechanism, it may be expected that by applying catalytic amounts of malonates, applicability of the system can be expanded and the radiochemical yield can be improved for a number of cases. Experiments into this topic are now in progress in our laboratories.

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Table I. Preparation of carboxyl-labelled carboxylic acids

Starting salt	Temp °C	Time min	Chemical	Yield % Chemical	Yield % Radiochemical
Sodium					
1. Acetate	400	120	CH_3–$^{14}COOH$	85	70
2. Propionate	390	120	C_2H_5–$^{14}COOH$	96	83
3. Butyrate	420	60	C_3H_7–$^{14}COOH$	88	70
4. i-Butyrate	430	120	$(CH_3)_2CH$–$^{14}COOH$	85	65
5. Cyclopentanone carboxylate	430	60	$(CH_2)_4CH$–$^{14}COOH$	91	55
6. Cyclohexane carboxylate	420	120	$(CH_2)_5CH$–$^{14}COOH$	96	80
7. Phenylacetate	290	120	C_6H_5–CH_2–$^{14}COOH$	88	76
Potassium					
8. Acetate	410	60	CH_3–$^{14}COOH$	98	88
9. Propionate	400	60	C_2H_5–$^{14}COOH$	90	83
10. Butyrate	420	60	C_3H_7–$^{14}COOH$	85	75
11. i-Butyrate	440	120	$(CH_3)_2$–CH_2–$^{14}COOH$	78	61
12. i-Valerate	440	120	$(CH_3)_2CH_2CH$–$^{14}COOH$	95	76
13. Caproate	400	60	$CH_3(CH_2)_4$–$^{14}COOH$	95	78
14. i-Caproate	420	120	$(CH_3)_2CH(CH_2)_2$–$^{14}COOH$	90	70
15. Laurate	420	120	$CH_3(CH_2)_{10}$–$^{14}COOH$	95	75
16. Elaidinate	380	120	$CH_3(CH_2)_7$–CH ‖ $CH(CH_2)_7$–$^{14}COOH$	85	69
17. Palmitate	340	120	$CH_3(CH_2)_{14}$–$^{14}COOH$	96	76
18. Phenylacetate	280	120	$C_6H_5CH_2$–$^{14}COOH$	91	80
19. β-Phenyl-propionate	380	60	$C_6H_5CH_2CH_2$–$^{14}COOH$	85	70
20. p-Cl-phenyl-acetate	290	100	p–Cl–$C_6H_4CH_2$–$^{14}COOH$	81	74
21. Succinate	420	60	$(CH_2)_2(^{14}COOH)_2$	73	58
22. Glutarate	440	60	$(CH_2)_3(^{14}COOH)_2$	80	52
23. Adipate	440	60	$(CH_2)_4(^{14}COOH)_2$	90	35
24. Pimelate	420	60	$(CH_2)_5(^{14}COOH)_2$	86	60

EXPERIMENTAL

Na and K salts were prepared by neutralization of an aqueous soln (or suspension) of the acid with equimolar amount of NaOH or KOH. The soln was evaporated and the residue dried *in vacuo* at 200° for 2 h.

In all cases, shown in the Table, the starting mixture was: 10 mM R–COOM + 1 M $^{14}CO_2$ or 5 mM R–$(COOM)_2$ + 1 mM $^{14}CO_2$ (spec. act.: $1{\cdot}88 \times 10^7$ dpm/mM).

Chemical yields were determined by isotope dilution method for an aliquot part of the aqueous salt soln.

Radioactive samples were dissolved in a dioxane scintillator and a Packard Tri-Carb scintillation spectrometer Model 574 was used to count the samples.

General procedure of preparation. In a tube $^{14}CO_2$ was distilled to the salt with liquid nitrogen. It was sealed and placed in a metal bath and kept at an appropriate temp. The $^{14}CO_2$ pressure was about 4–5 atm at the reaction temp. The system was opened and $^{14}CO_2$ recovered in the form of $Ba^{14}CO_3$. For measurement of the radioactivity the salts were converted into a p–Br–phenacyl ester derivatives; in some cases the acids were prepared from the aqueous solution of salts (run 5–7, 15–24).

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