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HOMOLYTIC DECARBOXYLATION OF GLUTAMATE ANALOGUES

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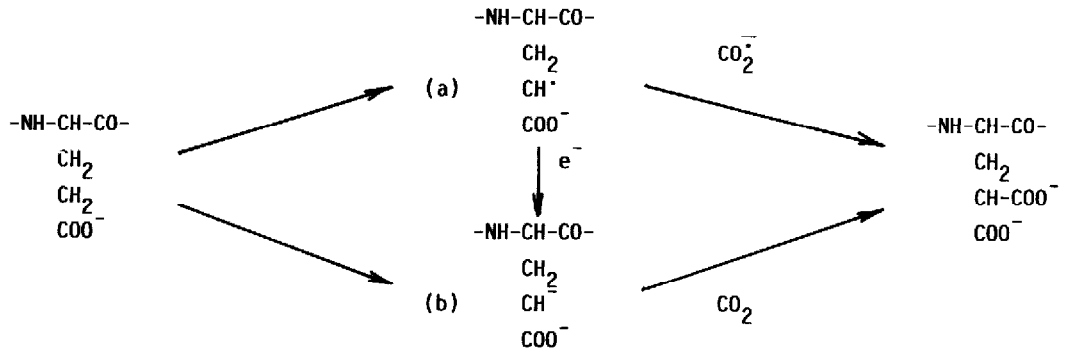
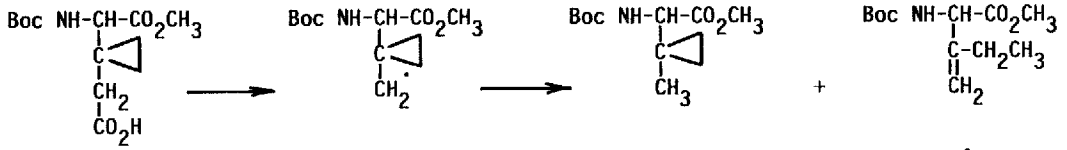
Abstract : The homolytic decarboxylation of a 3-cyclopropylglutamate derivative yields some rearrangement product whereas that of a 3-fluoroglutamate derivative yields the decarboxylation product without elimination. These results are discussed in relationship with the study of vitamin K-dependent carboxylation.

The mechanism of the post-ribosomal carboxylation of glutamyl residues catalyzed by vitamin K[1,2] is still obscure. Two intermediates can be *a priori* involved : a radical (a) and a carbanion (b).



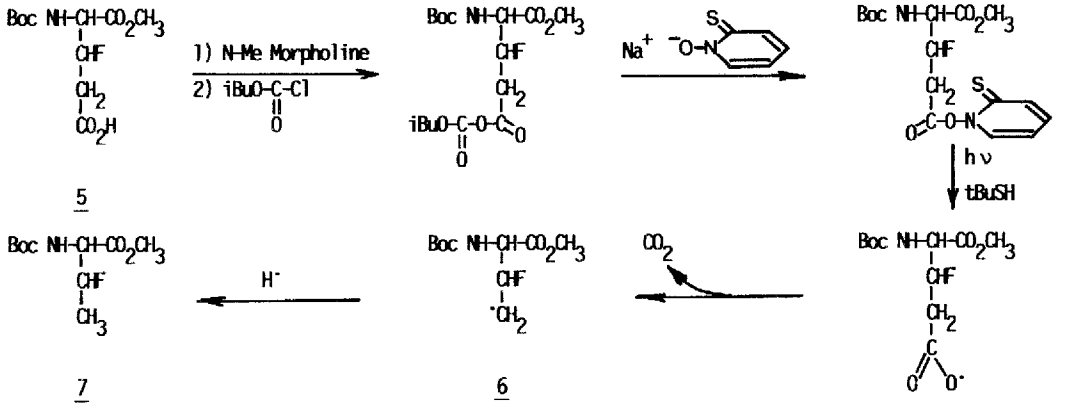
We synthesized two glutamate analogues designed to probe the occurence of intermediate (a) or (b) during the enzymatic reaction. Here, we test the basis of our working hypotheses on the reactivity induced by the functionnality of these analogues.

A positive argument for a radical would be the rearrangement of a cyclopropyl analogue[3,4], for instance compound 1[5] during the enzymatic carboxylation. Here, we show that radical 2, generated from 1 by homolytic decarboxylation according to Barton[8], actually rearranges : it reacts[9] with H· to yield the simple decarboxylation product 3[10] (49 %) and rearranges to give 4[11] (23 %).



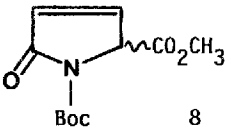
1 2 3 4

Alternatively, in order to characterize a carbanion we planned to use 3-fluoroglutamates : a carbanionic intermediate should lead to the elimination of the fluorine α to the carbanion as an anion, along with the formation of a dehydro compound. The β-elimination of fluoride has been used extensively in the design of k_{cat} inhibitors[12]. It has also been used to probe the mechanism of propionyl-CoA carboxylase[13] and recently we observed such an elimination during the decarboxylation of *erythro* 3-fluoroglutamate by glutamate decarboxylase[14]. However to be conclusive, this implies that a radical intermediate would not yield a dehydro compound through fluorine atom elimination. In contrast with the β-elimination of a fluoride anion, the lack of β-elimination of a fluorine atom, which could be predicted on the basis of the high energy required for the homolytic cleavage of a carbon-fluorine bond[15], was poorly documented, except a paper by Barton et al.[16] and a recent observation by De Clerq et al.[17]. It was thus necessary to ascertain this point by studying the fate of an α-fluoro radical generated under controlled conditions : both *threo* and *erythro* Boc-3-fluoroglutamate α methyl esters 5[18] were submitted to decarboxylation according to Barton[8].

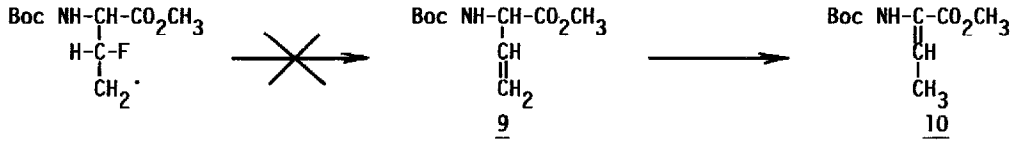


5 7 6

Radical mediated decarboxylation of Boc-3-F-glutamates[9]

Isomer	Boc NH-CH-CO$_2$CH$_3$ CHF CH$_3$ 7 %	 8 %
2R,3S 5e (erythro)	35	12
2R,3R 5t (threo)	11	20

In addition to decarboxylation products 7e and 7t[19], we observed the formation of 8[20]. The low yield of decarboxylated material could be explained by H· capture competitively with the decarboxylation. This suggests that the presence of fluorine slows down the formation of a radical on the neighbouring carbon. Nevertheless, the main result for our discussion is that the dehydroproduct 10[21], which could have been formed by F· elimination and isomerisation in the basic medium, was not observed.



The radicals possibly formed from 1 and 5 by the enzyme have an extra carboxyl group in α. We should have studied the decarboxylation of the corresponding malonic acids. To our knowledge, Barton's method[8] has not been applied to malonic acids and our attempts to decarboxylate benzylmalonic acid failed. However there is, so far, no evidence, that an α carboxyl group which has a stabilizing effect[22], should favor the F· elimination.

We have studied recently the interaction of the carboxylase with 5 and observed that 5e yields the elimination product[23]. The results obtained here strongly suggest that a carbanion is involved. Work with the cyclopropyl derivative 1 is in progress.

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5. Treatment of 2-t-butyloxycarbonylamino-3-methyleneglutarate 1-methyl-5-benzyldiester[6] with diazomethane in excess in diethylether, in the presence of palladium acetate according to Suda[7] yielded 1-benzyloxycarbonylmethyl-1-[t-butyloxycarbonylamino-methoxycarbonyl-methyl]-cyclopropane in 37% yield after column purification. Hydrogenolysis (H_2, 10 % Pd/C, methanol) afforded 1. F = 135-136°C. ^1H NMR ($CDCl_3$) 0.71 (bd, 4H, CH_2-CH_2), 1.42 (s, 9H, tBu), 2.42 (AB, 2H, δ_A = 2.25, δ_B = 2.59, J_{AB} = 16, CH_2), 3.73 (s, 3H, OCH_3), 3.85 (bm, 1H, CH), 5.10 (b signal, 1H, CO_2H), 5.87 (b signal, 1H, NH).
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9. Decarboxylation general procedure : The acid (0.19 M in dry DMF, -15°C) was treated with N-methylmorpholine (1 eq), isobutylchloroformate (1 eq) and after 5 min with N-hydroxypyridine-2-thione (1,17 eq). After 20 min, 2-methyl-2-propanethiol (10 eq) was added and the mixture irradiated with two 100 W tungsten lamps for 1 h at 0°C. Decarboxylation of Boc Glu-OBz yields benzyl 2-t-butyloxycarbonylamino-butanoate (90 %).
10. 3. ^{1}H NMR ($CDCl_3$) 0.35-0.80 (m, H, cyclopropyl), 1.05 (s, 3H, CH_3), 1.50 (s, 9H, tBu), 3.75 (s, 4H, OCH_3 + H), 5.20 (m, 1H, NH).
11. 4. ^{1}H NMR ($CDCl_3$) 0.90 (t, 3H, CH_3, J = 7), 1.50 (s, 9H, tBu), 2.15 (q, 2H, CH_2, J = 7), 3.80 (s, 3H, OCH_3), 4.78 (d, 1H, CH, J = 8), 5.08 (d, 2H, CH_2=), 5.30 (m, 1H, NH).
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19. The reaction was performed under a N_2 stream and the resulting CO_2 bubbled in baryum hydroxide. The baryum carbonate was filtered off and weighted.
7 : ^{1}H NMR ($CDCl_3$) *erythro* 1.42 (s, 9H, tBu), 1.30-1.60 (m, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.35 (ddd, 1H, H_2, $J_{H_2\,H_3}$ =3.5, $J_{H_2\,NH}$ = 9.2, $J_{H_2\,F}$ = 24.2), 4.85 (md, 1H, H_3, $J_{H_3\,F}$ = 45.7), 5.30 (d, 1H, NH) ; *threo* 1.45 (s, 9H, tBu), 1.20-1.60 (m, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.40 (dd, 1H, H_2, $J_{H_2\,H_3}$ = 10, $J_{H_2\,F}$ = 31.4), 4.80-5.50 (m, 2H, H_3 + NH).
20. 8, that was devoided of optical activity, resulted from lactamization and elimination of HF and migration of the double bond.
21. 10 was prepared from 7 by eliminating HF (EtONa/DMF). ^{1}H NMR ($CDCl_3$) 1.45 (s, 9H, tBu), 1.80 (d, 3H, CH_3, J = 7.1), 3.75 (s, 3H, OCH_3), 5.95 (m, 1H, NH), 6.65 (q, 1H, CH=, J = 7.1).
We checked that 10 would have been detected in our working conditions.
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