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# SELECTIVE γ-HYDROGEN ATOM ABSTRACTION IN REACTIONS OF N-ACETYLAMINO ACIDS AND N-ALKYLACETAMIDES WITH TITANOUS ION AND HYDROGEN PEROXIDE

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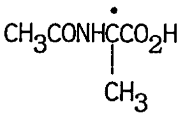
SUMMARY: Whereas reactions of N-acetylglycine, N-acetylalanine, and pyroglutamic acid, with $TiCl_3/H_2O_2$ in a flow system give e.p.r. spectra arising from the corresponding α-centred radicals (1-3), reactions of N-acetylvaline, 2-acetamidobutyric acid, N-propylacetamide, and N-(2-methylpropyl)-acetamide, give spectra arising from the respective γ-centred radicals (4-7). Production of the γ-centred radicals (4-7) is attributed to complexation of titanium to the amide group of the substrates.

As part of an investigation of free radical reactions of amino acid derivatives, we undertook an e.p.r. study of radicals formed in a flow system by the interaction of N-acetylamino acids with titanous chloride-hydrogen peroxide generated hydroxyl radical, using the method of Dixon and Norman.[1] The spectra were recorded at room temperature on a Varian E9 e.p.r. spectrometer. Spectral parameters are listed in the Table.

As expected on the basis of previous work,[2] N-acetylglycine and N-acetylalanine gave spectra consistent with formation of the corresponding α-centred radicals (1) and (2).

$CH_3CONH\dot{C}HCO_2H$

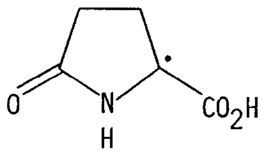
(1)



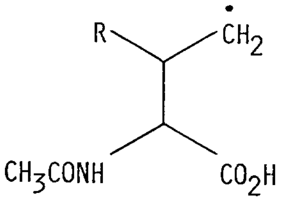
$CH_3CONH\dot{C}(CH_3)CO_2H$

(2)

No other signals were detected in the spectrum from N-acetylalanine. In the spectrum from N-acetylglycine, however, relatively low intensity signals consistent with the radical resulting from decarboxylation, i.e., $CH_3CONH\dot{C}H_2$,[3,4] were also observed. Decarboxylation of dicarboxylic acids with $TiCl_3/H_2O_2$ has been reported previously,[5] and formation of $CH_3CONH\dot{C}H_2$ by irradiation of N-acetylglycine in the presence of transition metal ions has already been noted.[3]

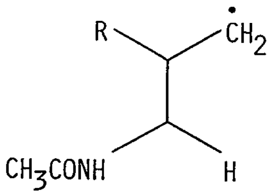


(3)



(4) R=Me

(5) R=H



(6) R=H

(7) R=Me

The e.p.r. spectrum obtained from reaction of pyroglutamic acid is consistent with formation of the corresponding α-centred radical (3). No other signals were detected in the spectrum.

N-Acetylvaline and 2-acetamidobutyric acid gave e.p.r. spectra indicating formation of the corresponding γ-centred radicals (4) and (5). No other signals were detected in the spectrum from N-acetylvaline. With 2-acetamidobutyric acid, other partially obscured, relatively low intensity signals were observed. These signals may be attributed to the radical resulting from decarboxylation. The e.p.r. spectrum obtained from a 1:1 (W/W) mixture of N-acetylglycine and N-acetylvaline showed signals for the γ-centred radical (4) derived from N-acetylvaline and the α-centred radical (1) derived from N-acetylglycine in the ratio _ca._ 10:1.

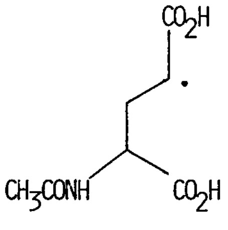
It is unlikely that observation of the γ-centred radicals (4) and (5) is facilitated by preferential reaction of other radicals with titanous ion or hydrogen peroxide,[6,7] as only the α-centred radicals (2) and (3) were observed with N-acetylalanine and pyroglutamic acid, respectively. It appears, therefore, that N-acetylvaline and 2-acetamidobutyric acid react by selective γ-hydrogen atom abstraction.

There is much evidence that the free hydroxyl radical is the active species in oxidations with $TiCl_3/H_2O_2$.[8] It is difficult, however, to attribute selective formation of the γ-centred radicals (4) and (5) to reactions involving free hydroxyl radicals. The selectivity may be attributed to reaction through complexation of titanium to the amide group of substrates. Moderately selective β-hydrogen transfer in reactions of carboxylic acids with $TiCl_3/H_2O_2$ has been attributed to reaction through a complexation of titanium to the carboxyl group.[9] We postulate complexation to the amide group of the substrates, rather than the carboxyl group, in light of our observations that N-propylacetamide and N-(2-methylpropyl)-acetamide give e.p.r. spectra consistent with formation of the γ-centred radicals (6) and (7), respectively.

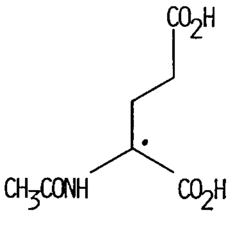
Table. ESR Parameters for Radicals (1-9)

| Substrate | Radical | Hyperfine Coupling Constants |
|---|---|---|
| N-Acetylglycine | (1)[2] | 16.5G, a(α-H) (d)<br>2.5G, a(N) (t) |
| N-Acetylalanine | (2)[2] | 16.5G, a(β-H) (q)<br>2.0G, a(N) (t) |
| Pyroglutamic acid | (3)[10] | 22.5G, a(β-H) (t)<br>3.0G, a(γ-H) (t)<br>2.5G, a(N-H) (d) |
| N-Acetylvaline | (4) | 27.5G, a(β-H) (d)<br>22.0G, a(α-H) (t) |
| 2-Acetamidobutyric acid | (5) | 26.0G, a(β-H) (t)<br>22.5G, a(α-H) (t) |
| N-Propylacetamide | (6) | 27.5G, a(β-H) (t)<br>22.0G, a(α-H) (t) |
| N-(2-Methylpropyl)-acetamide | (7) | 27.5G, a(β-H) (d)<br>21.5G, a(α-H) (t) |
| N-Acetylglutamic acid | (8) | 21.0G, a(β-H) (t)<br>21.0G, a(α-H) (d) |
|  | (9) | 22.5G, a(β-H) (t)<br>4.0G, a(N) (t) |

N-Acetylglutamic acid gave a spectrum consistent with formation of the γ-centred radical (8) and the α-centred radical (9) in the ratio *ca.* 1:1. The corresponding β-centred radical was not detected.



(8)



(9)

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