

Regioselectivity in Formations of Amidocarboxy-substituted Free Radicals

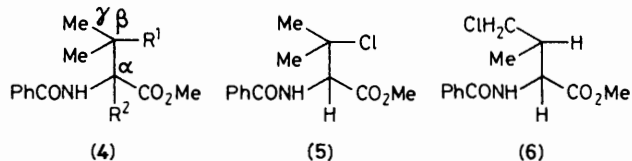
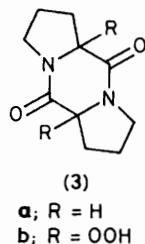
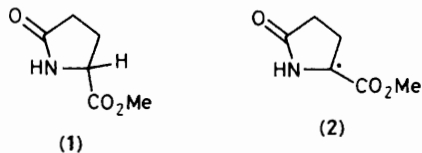
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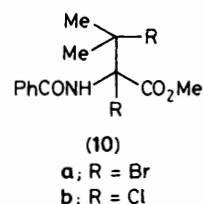
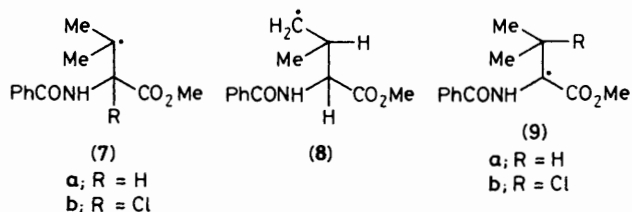
Deuterium isotope effects establish a direct contrast in regioselectivity in reactions of *N*-benzoylvaline methyl ester with sulphuryl chloride and *N*-bromosuccinimide, and are indicative of factors affecting production of amidocarboxy-type captodative free radicals.

There have been two reports of regioselective hydrogen-atom transfer reactions affording amidocarboxy-substituted radicals. Irradiation of a mixture of methyl pyroglutamate (**1**) and di-*t*-butyl peroxide afforded products attributed to dimerization of the radical (**2**),¹ and oxidation of (**3a**) gave the diperoxide (**3b**).² We reported recently that reaction of

N-benzoylvaline methyl ester (**4a**) with sulphuryl chloride gave the β -chlorovaline (**5**) and lesser amounts of diastereoisomers of the γ -chloro derivative (**6**).³ This result is at variance with the earlier work as it indicates that the radicals (**7a**) and (**8**), intermediates in the reactions to give (**5**) and (**6**) respectively,⁴ are formed in preference to the amidocarboxy-



a; R¹ = R² = H
b; R¹ = D, R² = H
c; R¹ = H, R² = D



substituted radical (**9a**). This discord prompted our present study of the reaction of (**4a**) and the deuteriated analogues (**4b**) and (**4c**)† with sulphuryl chloride, and of the free-radical reaction of (**4a–c**) with *N*-bromosuccinimide (NBS).⁵

In measuring the relative rates of reaction of (**4a–c**) we exploited their chirality. The enantiomers exhibit identical reactivity, but are physically separable by g.l.c. on a Chrompack XE-60-S-VAL-S-X-PEA column. Thus we were able to measure the relative rates of consumption of (**4a–c**) from mixtures, for example, of the 2*R*-valine (**4a**) and the 2*S*-valine (**4b**). The ratios of the rate constants for the reactions of (**4a–c**) with sulphuryl chloride and NBS were calculated from the relative rates of consumption of (**4a–c**)⁶ and these are presented in Table 1.

The relative rate constants for reaction of (**4a–c**) with sulphuryl chloride establish that there is a deuterium isotope effect for β-C–H bond cleavage, but no isotope effect for α-C–H bond cleavage. In direct contrast, the reaction with NBS exhibits no deuterium isotope effect for β-C–H bond cleavage, but there is an effect for α-C–H bond cleavage. These results establish that cleavage of the β-C–H bond is the irreversible rate-determining step in the reaction with sulphuryl chloride, whereas cleavage of the α-C–H bond is the irreversible rate-determining step in the reaction with NBS. We propose that the most reasonable interpretation of these results is that the chlorination involves hydrogen-atom abstraction from the β-position of (**4**) with subsequent chlorine incorporation to give (**5**),‡ whereas the reaction with NBS proceeds *via* hydrogen-atom abstraction from the α-position of (**4**) and yields the dibromide (**10a**), the final product of the reaction with NBS.

Variations of selectivity in hydrogen-atom transfer reactions have been reviewed by Russell.⁷ The contrast of regioselectivity observed in the reactions with sulphuryl chloride and NBS may be interpreted in terms of the relative degrees of C–H bond homolysis in the transition states of these reactions. The greater deuterium isotope effect for α-C–H bond cleavage in the reaction with NBS compared to the effect for β-C–H bond homolysis in the chlorination

† All new compounds were fully characterised.

‡ We assume that the γ-chloro derivative (**6**) is produced by hydrogen-atom transfer from the γ-position of (**4**) with subsequent chlorine incorporation. Because of this alternative reaction pathway the deuterium isotope effect for β-C–H bond homolysis would be moderately higher (*ca.* 30%) than indicated by the relative rates of reaction of (**4a**) and (**4b**).

Table 1. Relative rates of reaction of the valines (**4a–c**).

Valine	Reagents	
	Sulphuryl chloride ^a	NBS ^b
(4a)	1.0 ^c	1.0 ^c
(4b)	1.25 ± 0.05	1.00 ± 0.03
(4c)	1.00 ± 0.03	3.70 ± 0.20

^a Valine and sulphuryl chloride in benzene under nitrogen. Reaction at reflux catalysed by benzoyl peroxide or irradiation. ^b Valine and NBS in CCl₄ under nitrogen. Reaction at reflux catalysed by benzoyl peroxide or irradiation. ^c Assigned as unity for each reagent.

reaction indicates a greater degree of bond homolysis in the transition state of the former. With little development of radical character in the transition state of the chlorination reaction, the regioselectivity in this case is controlled by the inductive electron-withdrawing effect of the amido and carboxy groups acting to retard attack at the adjacent α-position by electrophilic radicals involved in the hydrogen-atom abstraction. The reaction with NBS is more sensitive to radical-stability effects since there is a greater degree of development of radical character in the transition state. Hydrogen-atom transfer from the α-position is favoured, therefore, because the product is the capto-dative radical (**9a**), stabilized by the synergistic effect of resonance electron-donating amido and electron-withdrawing carboxy groups.⁸

In a related system the dichloride (**10b**) reacted with tri-*n*-butyltin hydride to give the β-chlorovaline (**5**) in almost quantitative yield. Reductions of alkyl halides by organotin hydrides proceed by halogen-atom abstraction with subsequent hydrogen incorporation. In these reactions stability of the free-radical intermediate is the prime factor in determining the rate of halogen-atom abstraction.⁹ Thus the production of (**5**) from (**10b**) implies that the capto-dative radical (**9b**) is more stable than the tertiary radical (**7b**). Further, the production of only trace amounts of (**4a**), the product of

subsequent reduction of (5),¹⁰ in the reaction with tri-n-butyltin hydride establishes that the rate of halogen-atom abstraction from (10b) to give (9b) is at least three orders of magnitude faster than the rate of halogen-atom transfer from (5) to give (7a). This implies the greater relative stability of the capto-dative radical (9b) compared with (7a).

These results support our conclusion that the contrast in regioselectivity in the reactions of *N*-benzoylvaline methyl ester (4) with sulphuryl chloride and NBS can be attributed to the respective degrees of C-H bond homolysis in the transition states of these reactions. Extensive bond homolysis and development of radical character in the transition state of the reaction of (4) with NBS results in reaction via α -C-H bond homolysis to give the stabilized radical (9a), whereas the lack of development of radical character in the transition state of the reaction of (4) with sulphuryl chloride is manifest in regioselectivity determined by inductive effects and resulting in β -C-H bond homolysis. The amidocarboxy-type capto-dative radicals (9a) and (9b) are considerably more stable than, for example, the tertiary radicals (7a) and (7b), but hydrogen-atom transfer reactions may afford less-stable products if electrophilic radicals are involved in the hydrogen-atom abstraction and if there is little development of radical character in the reaction transition state.

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