Preferential Reactivity of Glycine Residues in Free Radical Reactions of Amino Acid Derivatives

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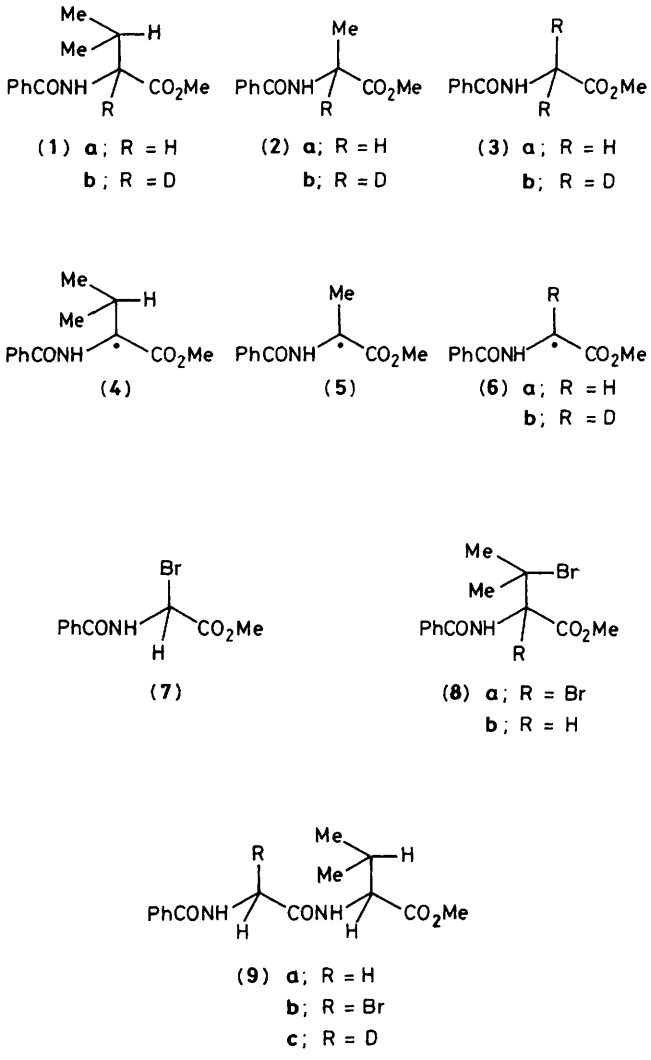
Reactions of amino acid derivatives, including a novel synthetic procedure for direct and selective functionalisation of glycine derivatives, indicate that the particular reactivity of glycine residues in free radical reactions is due to the stability of the radicals produced by their atom transfer reactions.

Preferential reactivity of glycine residues in free radical reactions of proteins, peptides, and other amino acid derivatives has been attributed to selective hydrogen atom abstraction from the α-carbon of the glycine moieties.[1] This selectivity is contrary to the expectation that tertiary radicals should be formed in preference to secondary ones.[2] Glycine residues afford secondary radicals by α-C–H bond homolysis, whereas analogous reactions of derivatives of other amino acids produce tertiary radicals. We have studied reactions of derivatives of glycine, alanine, and valine to examine this hitherto unexplained reactivity of glycine derivatives.

Relative rates of reaction of (**1a**), (**2a**), and (**3a**), and of the



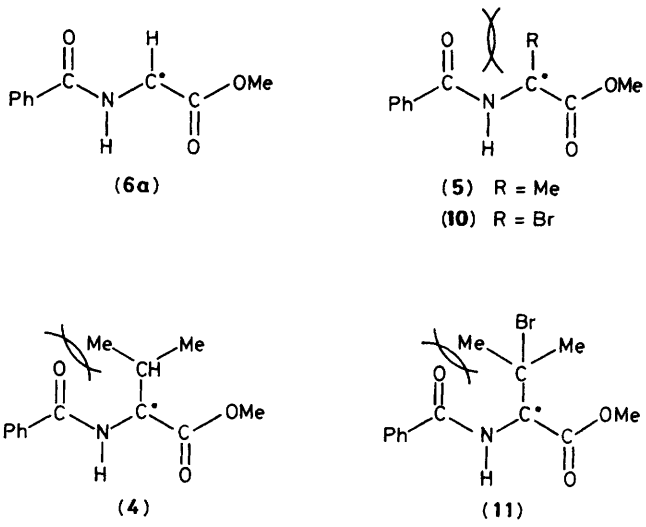


Figure 1

Table 1. Relative rates of reaction of the amino acid derivatives (**1**)—(**3**) with NBS.[a]

Valine (**1a**)	1[b]	(**1b**)	0.27 ± 0.02[c]
Alanine (**2a**)	7.7 ± 1.1	(**2b**)	4.1 ± 0.40
Glycine (**3a**)	23 ± 3.5	(**3b**)	7.3 ± 1.5

[a] Reaction under nitrogen in refluxing carbon tetrachloride, catalysed by irradiation. [b] Assigned as unity. [c] In ref. 3, the relative rate constants were reported incorrectly as their reciprocals.

deuteriated analogues (**1b**), (**2b**), and (**3b**),† with *N*-bromosuccinimide (NBS) were determined using methods described previously[3] and these are presented in Table 1. Based on our earlier studies[3] of atom transfer reactions of (**1**) and the deuterium isotope effects observed in these reactions of (**2**) and (**3**), we propose that the relative rates of reaction of (**1a**)—(**3a**) reflect the ease of hydrogen atom abstraction from the α-positions of these compounds. Thus our results show that hydrogen atom transfer from the glycine derivative (**3a**) to give the secondary radical (**6a**) is faster than production of the tertiary radicals (**4**) and (**5**) in similar reactions of (**1a**) and (**2a**) respectively.

Since hydrogen atom abstractions in reactions with NBS are selective for production of the most stable product radical,[4] our results indicate that, in direct contrast to expectation, the secondary radical (**6a**) is marginally more stable than the tertiary radical (**5**), and both (**6a**) and (**5**) are considerably more stable than (**4**). We attribute this peculiar stability of the radical (**6a**) to a particularly favourable geometry. Stabilization of the captodative[5] radicals (**4**)—(**6**) will result from overlap of the semi-occupied p orbitals with the π orbitals of the amido and methoxycarbonyl substituents. There will be maximum overlap of these orbitals in planar conformations of the radicals (**4**)—(**6**), Figure 1. The radical (**5**) will be destabilized compared to (**6a**) by non-bonding interactions associated with planar conformations of (**5**), and (**4**) will be even less stable owing to more severe non-bonding interactions. These destabilizing influences outweigh the normal thermodynamic preference for the production of tertiary radicals.

The reaction of the glycine derivative (**3a**) with NBS gave the monobromide (**7**) in high yield, presumably by bromine atom transfer to (**6a**). The lack of subsequent reaction of (**7**) is consistent with our rationale for the reactivity of (**3**). The radical (**10**) (Figure 1) produced by hydrogen atom abstraction from (**7**) would be less stable than (**6a**) because of non-bonding interactions.

In a related system we have examined reactions of the monobromoglycine derivative (**7**) and the dibromovaline derivative (**8a**) with tri-n-butyltin in hydride. The dibromovaline derivative (**8a**) is the final product of reaction of (**1a**) with NBS. Reaction of (**8a**) with tri-n-butyltin hydride affords the monobromovaline derivative (**8b**)[6] and (**3a**) is produced from (**7**). These reactions are expected to proceed by halogen atom abstraction with subsequent hydrogen incorporation, and the stability of the free radical intermediate is the prime factor in determining the rate of halogen atom abstraction.[7] From mixtures of (**7**) and (**8a**) we achieved selective reduction of (**7**) to (**3a**), which we take to indicate the greater relative stability of the radical (**6a**) compared to (**11**). This is not surprising when the non-bonding interactions in (**6a**) and (**11**) are compared (Figure 1).

We conclude that the selective reaction of glycine residues

† All new compounds were fully characterised.

in these and other[1] free radical reactions of amino acid derivatives is due to the stability of the radicals produced by atom transfer reactions. Radicals produced by similar reactions of other amino acid derivatives are relatively unstable because of non-bonding interactions. Reactions with NBS provide a viable synthetic procedure for direct and selective functionalisation of glycine derivatives. Accordingly, treatment of the dipeptide (**9a**) gave the bromide (**9b**) in high yield. Subsequent reaction with triphenyltin deuteride produced the regioselectively-labelled dipeptide (**9c**).

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