Investigations on the Mechanism of Racemization of *N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteine Active Esters in Non-polar Solvents

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Summary *N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteine pentachlorophenyl ester has been found to racemize in a non-polar solvent without deuterium exchange of the α-hydrogen in the presence of triethylamine.

RECENTLY we reported that the racemization of *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteine active esters by abstraction of the α-proton is considerable during the synthesis of peptides and sequential polypeptides if triethylamine is present.[1] Any racemization which occurs during polypeptide synthesis would be permanently incorporated in the polymer and impossible to separate by known procedures. We now report further investigations on the mechanism of racemization.

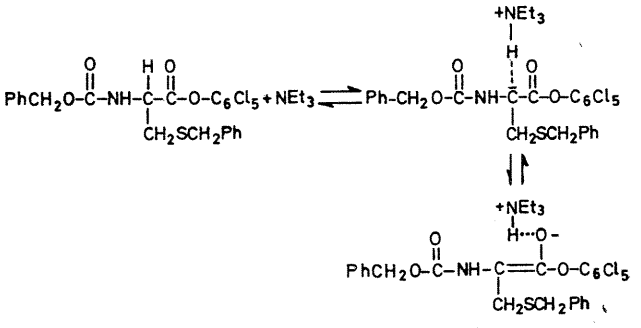
Ford and Cram[2] have reported that the stereochemistry of a racemization reaction can be derived from the relative exchange (k_e) and racemization (k_α) rates.† Racemization of amino-acid and peptide derivatives with strong bases such as hydroxide and alkoxide in polar solvents has been demonstrated to parallel exchange of the α-hydrogen.[3] However, in non-polar solvents, which are frequently used in peptide synthesis, the mechanism of racemization of *N*-benzyloxycarbonyl-amino-acid active esters has not been investigated.

N-Benzyloxycarbonyl-*S*-benzyl-L-cysteine pentachlorophenyl ester was racemized in chloroform with 7 equiv. of NEt_3 in the presence of 50 equiv. of MeOD. The reaction mixtures were kept at room temperature for 2—7 h, the reaction was then quenched by the addition of 20% deuterium sulphate. The organic phase was washed with distilled water until neutral and dried over anhydrous magnesium sulphate. The chloroform was removed *in vacuo* and the residue was redissolved in tetrahydrofuran–methanol to back-exchange the amide proton. The solvent was removed *in vacuo* and the solid residue was

† According to Ford and Cram,[2] the values of the ratio, k_e/k_α, can be $\gg 1$ for retention with exchange, 1 for racemization with exchange, 0·5 for inversion with exchange, and $>0{\cdot}5$ for inversion or racemization without exchange.

triturated with pentane and removed by filtration. The isolated *N*-benzyloxycarbonyl-*S*-benzylcysteine pentachlorophenyl ester analysed correctly for C, H, N, and Cl. The deuterium content was determined by m.s. analysis of the acylium ions (*m/e* 328 and 329) formed upon electron impact with the active ester and compared with the degree of racemization. The ratio of the rate constants, k_e/k_α, for the 2 h runs were determined using equation (1).

$$k_e/k_\alpha = \frac{\ln [1 - \text{fraction of deuteriated } PhCH_2OCONHCD(CH_2SCH_2Ph)CO_2C_6Cl_5]}{\ln [1 - \text{fraction of racemic } PhCH_2OCONHCH(CH_2SCH_2Ph)CO_2C_6Cl_5]} \quad (1)$$



SCHEME

The values of this ratio for three parallel experiments were 0·055, 0·054, and 0·060. In the 7 h experiment the racemization was almost complete but only 20% of the α-hydrogen was exchanged. These results suggest that the racemization of *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteine active esters by α-hydrogen abstraction probably occurs through a "conducted-tour mechanism"[4] as indicated in the Scheme. This is the first time that this mechanism has been suggested for racemization of an asymmetric centre adjacent to a carbonyl function and the first time it has been noted for the racemization of amino-acid derivatives.

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