Stereospecific Oxidation of Methionine to Methionine Sulphoxide by Tetrachloroauric(III) Acid

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Summary The use of gold(III) as oxidant provides a method for the stereospecific oxidation of methionine to methionine sulphoxide under conditions that can be extended to biological systems containing sulphides; preliminary kinetic studies give a possible explanation of the stereospecificity of this reaction.

Co-ordination of a thioether to gold(III) can be accompanied by reduction of Au^{III} to Au^{I} and simultaneous oxidation of the sulphide, especially in the presence of excess of ligand.[1,2] An analogous reaction is known to occur with phosphines, arsines, and stibines.[3] The nature of the products and the mechanism of oxidation has not yet been clarified but such a mild oxidation process should be of use in the modification of methionine residues which often play an important role in proteins and biologically active polypeptides.

Reaction of (*S*)-methionine§ (5×10^{-3} mol, in 20 ml H_2O)

§ The amino-acids have the L-configuration. The following abbreviations are used: Boc=t-butyloxycarbonyl, OEt = ethyl ester.

with an equimolar amount of $HAuCl_4$ gives, in a few minutes, a colourless solution, t.l.c. and amino-acid analysis showing complete absence of the starting amino-acid and the presence of the corresponding sulphoxide (no traces of sulphone were detected). Addition of acetone–ethanol (1 : 1 v/v) allowed this sulphoxide to be isolated in quantitative yield. The value of $[\alpha]_D^{25} + 132 \pm 1°$ (c 0·8; 1N-HCl) found corresponds to that of the (*S*)-methionine (*S*)-sulphoxide,[4] clearly indicating that the oxidative process occurred stereospecifically giving only one of the two possible diastereoisomers. The same results have been obtained in buffered solutions at pH 2, 3, and 5, and also using an excess of $HAuCl_4$. The formation of (*R*)-methionine (*R*)-sulphoxide starting from (*R*)-methionine has been established by performing the same reaction on (*RS*)-(54·5% *S* + 45·5% *R*)- and (65% *S* + 35% *R*)-methionine: the $[\alpha]_D^{25}$ values for the three mixtures correspond to the ratio of the two sulphoxide enanthiomers (*S*) — (*S*)/(*R*) — (*R*) = 1·00, 1·19, 1·86.

The reaction between peptides containing methionine (Boc-Ala-Met-Gly-OEt, Boc-Met-Gly-OEt, and Boc-Ala-Met-OEt)§ and $HAuCl_4$ showed that the oxidation at the sulphur atom also occurs when methionine is part of a peptide chain.

The kinetics of the oxidation were followed spectrophotometrically in acidic aqueous methanol at 25 °C ($[HClO_4] = 5 \times 10^{-2}$M, $[HAuCl_4] < 5 \times 10^{-5}$M; [(*S*)-Met] ranging from 2×10^{-2} to 10^{-3} M). The change of optical density with time at 320 nm takes place in two stages, in the first of which a considerable and rapid increase is observed. This is followed by a second step in which the absorbance decreases more slowly to zero. The first stage most probably corresponds to the formation of the sulphide complex $AuCl_3(Met)$[2,5] and the second to the reduction of the yellow Au^{III} complex to a colourless Au^{I} species. The first reaction is too fast to be followed by conventional techniques under these conditions. The rate of the reduction depends on [(*S*)-Met] and the pseudo-first-order rate constant obeys the relationship $k_{obs} = k$[(*S*)-Met]. This implies that a second methionine is required to promote the reduction of Au^{III} to Au^{I}. This behaviour was not completely unexpected since monosubstituted thioether complexes of the type $AuCl_3$ (R^1R^2S) are relatively stable, and $AuCl_3(PR_3)$ is reduced to $AuCl(PR_3)$ only in the presence of excess of phosphine. If it is possible to draw an analogy with the known structure of the {Pt[(*S*)-Met]Cl_2}[6] which contains equal amounts of (*R*) + (*S*) sulphur atoms, one might conclude that stereospecificity must arise from the interaction of two co-ordinated chiral centres when the second methionine becomes bonded to gold. The influence of an asymmetric co-ordinated ligand on the entering of a second one has been recently successfully employed for the resolution of racemates.[7]

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