Role of Methionine in the Facilitated Cleavage of Aromatic Ethers by Methanesulphonic Acid

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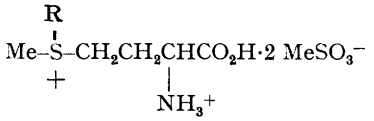
Summary Aromatic ethers, such as anisole or phenetole, were cleaved smoothly with methanesulphonic acid in the presence of methionine, which acted as an alkyl acceptor to form methionine *S*-methyl (or ethyl)sulphonium salt.

CURRENTLY we are examining the usefulness of the trifluoromethanesulphonic acid (TFMSA)–trifluoroacetic acid (TFA)–anisole system or the methanesulphonic acid (MSA)–anisole system for removal of all protecting groups employed at the

final step of peptide synthesis.[1,2] Among the amino-acid derivatives tested, recovery of Met from Z-Met-OH with these reagents was very low, because of the formation of a by-product, detectable on the short column of a Stein–Moore amino-acid analyser, eluted between His and ammonia.

When a mixture of Met and anisole in MSA was kept at 22 °C for 24 h, this by-product was isolated in quantitative yield as the sole product, recrystallizable from alcohol, and we report here its identification as the methionine salt (I) from i.r. and ^1H and ^{13}C n.m.r. data: ν_{max} (Nujol) 1715 cm^{-1}; δ (^1H) (D_2O), 2·40 (2H, m), 2·80 and 2·97 (6H, each s), 3·48 (2H, m), and 3·89 (1H, t, J 6 Hz); δ (^{13}C) (D_2O), 170·9 (CO), 51·9 (CH), 39·9 and 39·4 (each CH_2), and 25·5 and 25·2 (Me) p.p.m.† This structural assignment was confirmed by direct comparison (n.m.r. and i.r.) with an authentic sample of (I), derived from methionine *S*-methylsulphonium iodide[3] by treatment with MSA *via* the corresponding picrate.



(I) R = Me
(II) R = Et
(III) R = CH_2Ph

The most plausible origin of the methyl group in (I) was shown by the fact that the product formed by treatment of Met with 10% TFMSA–TFA in the presence of anisole was converted into (I), in the same manner as the iodide mentioned above. Thus the sulphur atom of Met trapped the methyl group of anisole as a cation. Similarly, the *S*-ethylsulphonium dimethanesulphonate (II) was obtained, when phenetole was used instead of anisole. Acidic cleavage of anisole or phenetole did not take place when Met was absent and, in addition, Met in these acids gave no observable side reactions in the absence of anisole or phenetole. Z-Met-OH and the MSA–anisole system still gave (I) as the major product. A small amount of the *S*-benzyl derivative (III) was also detected. Transfer of the methyl group from anisole to the sulphur atom of Met can be explained by the hard–soft acid–base concept;[4] *i.e.*, Me^+ has an appreciable affinity with sulphur, because of its softness.

This hitherto unknown reaction may possibly be applied to the hydrolytic cleavage of aromatic ethers, since anisole gave phenol with MSA–Met at room temperature in reasonable yield. In practical peptide syntheses, this side reaction can be prevented completely by the use of Met(O).[5] Thus endorphin, H-Tyr-Gly-Gly-Gly-Lys-Met-Gly-OH,[6] was obtained in good yield, by exposure of the protected heptapeptide, Z(OMe)-Tyr-Gly-Gly-Gly-Lys(Z)-Met(O)-Gly-OH, to the MSA–anisole system at 20 °C for 60 min, followed by reduction of the Met(O) residue with dithiothreitol.

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† Chemical shifts were measured with respect to internal dioxan and converted into the Me_4Si scale using the formula $\delta(Me_4Si) = \delta(\text{dioxan}) + 67{\cdot}4$ p.p.m.

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