Stereochemical Course of Methyl Transfer from Methanol to Methyl Coenzyme M in Cell-Free Extracts of Methanosarcina barkeri


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The majority of methanogens produce methane from CO₂ and H₂, however, some species, such as Methanosarcina barkeri, can utilize methanol, methylamines, or acetate acid to produce methane and cellular carbon compounds. The conversion of methanol to methane was originally thought to involve transfer of the methyl group to the carbonyl carbon of biotin, followed by reduction of the resulting methylocobalamin. However, more recent work, following the discovery of coenzyme M as a methyl carrier in methanogens, points to the involvement of two methyltransferases, MT₁ and MT₂, which convert CH₃OH to CH₃S-CoM followed by reduction of the latter to methane by methyl-CoM reductase. MT₁ is a corrinoid enzyme which requires reductive activation, and MT₂ can transfer the methyl group from a free or bound methylated corrin to coenzyme M. The conversion of CH₃OH to CH₃S-CoM, therefore, appears to involve two sequential transfers of the methyl group, each presumably occurring with inversion of configuration, predicting that the overall reaction proceeds with net retention of methyl group configuration. Alternate reaction sequences or mechanisms, e.g., free-radical intermediates, might result in opposite sterechemistry or in significant degrees of racemization.

To probe the steric course of methyl coenzyme M formation we synthesized (R)- and (S)-[H₁₃C] methanol from (S)- and (R)-[H₁₃C] acetate acid as shown in Scheme I. Samples of the methanol and the intermediate methylhydroxymethylium were degraded to methyl acid to determine their purity by using the chirality analysis method of Cornforth et al. and Arigoni and co-workers. It is evident from the data in Scheme I that the conversion of hydroxymethylium to methanol was accompanied by substantial racemization, probably due to the method employed in the synthesis of methyl group from p-methoxybenzoyl chloride by the p-meth-

Scheme I. Synthesis and Configurational Analysis of Chiral Methanol

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(11) Studies on a substantial number of different hydrogenases have provided convincing evidence that single transfer of methyl groups by Sₙ₂ processes proceed with inversion of configuration.


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of the methyl group of methyltetrahydrofolate to homocysteine, catalyzed by the B₁₂-dependent methionine synthase from *E. coli*, which we have demonstrated also occurs with net retention of methyl group configuration.²⁶ Both reactions pose the same question of how a relatively inert bond, the C–O bond of methanol in the present case or the C–N bond of methyltetrahydrofolate in the case of methionine synthase, is cleaved in the transfer of a methyl group.

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