Selenomethionine in Enzymatic Transmethylations

In the past, biological interest in selenium has been centred around its toxic role as the cause of 'alkali disease' and 'blind staggers'[1] and as a source of industrial poisoning[2]. However, recent developments suggest a more important role for this element. Thus, it has been shown that selenium is an essential trace element for the rat[3] and is stimulatory, if not essential, for the growth of certain plants[4]. While inorganic selenium compounds are active in these cases, there is evidence that these inorganic selenium compounds are converted biologically into organic compounds, including the selenium analogues of cysteine[5], cystine, methionine[6] and cystathionine[7]. The structure of the essential selenium compound or compounds, therefore, remains to be established.

These results have stimulated interest in the metabolic role of selenomethionine. This analogue has been shown to support exponential growth of a methionine-requiring *E. coli* mutant, growth continuing for as long as one hundred generations on a methionine-free medium containing selenomethionine. Furthermore, micro-organisms grown under these conditions are capable of adaptive enzyme formation[6,8]. These results are of particular significance in that they demonstrate that proteins in which methionine is replaced by its selenium analogue have retained their functional integrity.

In the light of these findings, it was considered of interest to investigate the ability of selenomethionine to replace methionine in a biological reaction in which the sulphur atom of this amino-acid is functionally involved, namely, transmethylation. As is well established, an adenosine triphosphate-dependent enzymatic activation resulting in the formation of S-adenosylmethionine is a prerequisite for the enzymatic transfer of the methyl group of methionine. S-adenosylmethionine can act as a methyl donor to a suitable methyl acceptor in the presence of specific methylpherases[9]. It may be recalled that an essential feature in the activation reaction is the conversion of the sulphur atom from a thioether to a sulphonium configuration.

When selenomethionine was incubated with methionine-activating enzyme prepared from rabbit liver[10] or yeast[11], it was utilized as well as or better than methionine. Fig. 1 shows the results of an experiment in which methionine and selenomethionine are compared as substrates for the yeast methionine-activating enzyme. In the presence of excess pyrophosphatase the reaction can be followed by measuring the amino-acid dependent mineralization of the three phosphates of adenosine triphosphate and/or the formation of an adenosyl compound which, because of its cationic nature, is not adsorbed on 'Dowex-1' Cl. It can be seen that, in fact, selenomethionine is a better substrate for the yeast-activating enzyme than the natural sulphur analogue.

To test the ability of Se-adenosylselenomethionine to serve as methyl donor, the adenosyl compound formed from selenomethionine was precipitated as the crystalline trireineckate derivative, converted to the sulphate salt and afterwards incubated with guanidoacetic acid in the presence of pig-liver creatine methylpherase[9]. It was found that 0·28 μmole of Se-adenosylselenomethionine supported formation of 0·21 μmole of creatine by transmethylation while a

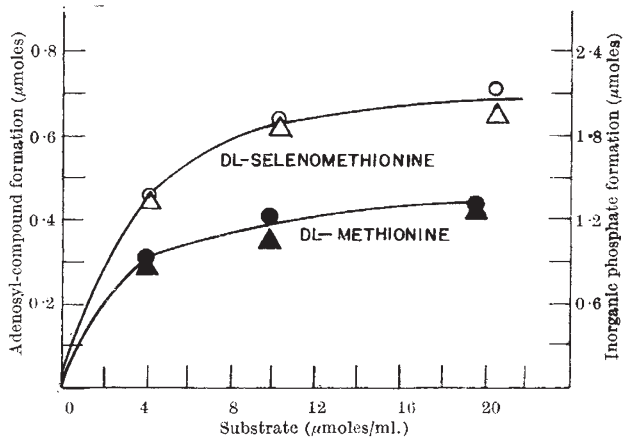

Fig. 1. Each vessel contained in a final volume of 0·5 ml.: *tris*(hydroxymethyl)aminomethane, *p*H 7·6, 75 μmoles; potassium chloride, 150 μmoles; magnesium chloride, 150 μmoles; adenosine triphosphate, neutralized with potassium hydroxide, 12 μmoles; reduced glutathione, neutralized with potassium hydroxide, 5 μmoles; substrate as indicated; an excess of yeast inorganic pyrophosphatase; 90 micrograms of methionine activating enzyme purified 250-fold from an extract of baker's yeast (ref. 11). Incubation was for 30 min. at 37°. The reaction was terminated by addition of perchloric acid and aliquots of the protein-free supernatant were used for determination of the inorganic phosphate (triangles) and adenosyl compound (circles) (ref. 10). A control was run without added substrate and the control value subtracted from the experimental. The stoichiometry of the reaction requires the mineralization of three moles of phosphate for each mole of adenosyl compound formed

control of 0·32 μmole of authentic S-adenosylmethionine gave a quantitative yield of creatine.

The ability of inorganic selenium compounds to function as methyl acceptors in fungi and related species has been demonstrated by the studies of Challenger and his school[12]. The experiments reported here emphasize the ability of selenomethionine to replace its natural sulphur analogue as a substrate in two enzymatic reactions involved in biological transmethylation. Although in one instance it has been found that selenomethionine competes with its sulphur analogue[13], it may be postulated on the basis of the present evidence that the ability of seleniferous compounds to replace their sulphur-containing analogues is rather widespread.

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