Transguanylation and Formation of 2-Aminothiazoline from *S*-(2-Aminoethyl)isothiourea

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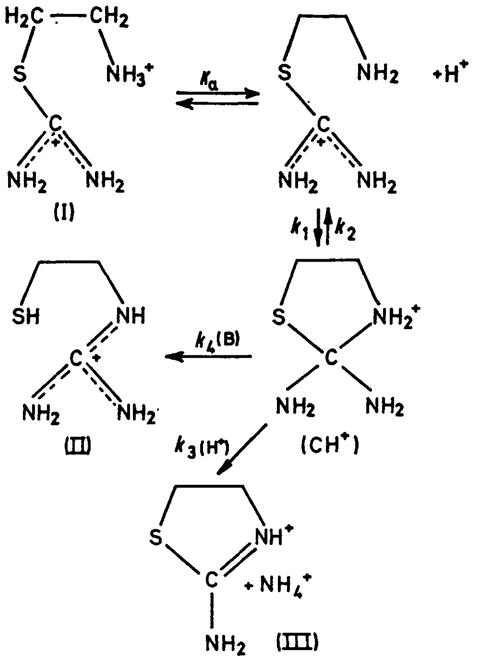
Summary The tripartite pH–rate profile obtained for disappearance of *S*-(2-aminoethyl)isothiourea indicates that a tetrahedral carbon addition intermediate occurs in the transformations of this system.

S-(2-AMINOETHYL)ISOTHIOUREA (I) is believed to provide radiation resistance in organisms by means of an intramolecular transguanylation reaction to yield 2-mercaptoethylguanidine (II), which has a free SH group. In addition to (II), which is produced in neutral aqueous solutions, dilute acid solutions of (I) yield 2-aminothiazoline (III) and ammonia as the main products.[1] From the results of quantitative ion-exchange and SH content studies at 0·09M-(I)[1] it can be calculated that (II) and (III) are produced in equal amounts at *ca.* pH 4·2. Due to the appearance of these two products from one starting material, it has been suggested that a cyclic tetrahedral carbon intermediate is formed.[1] Since the possible intermediate has an SH group and three amino-nitrogen atoms joined to the tetrahedral carbon, there is opportunity for a mechanistic study of a tetrahedral carbon intermediate with groupings different from, though related to, those studied previously. Related reactions, the mechanisms of which have been studied, include transacetylation from sulphur to nitrogen in *S*-acetylmercaptoethylamine,[2] hydrolysis of thioimidate esters to give thiolesters,[3] and the methoxy-aminolysis of methyl thiolformate.[4] In these three cases a diffusion-controlled proton transfer reaction is rate determining under some conditions.



The occurrence of a tetrahedral addition intermediate in the transformations of (I) is indicated by the tripartite pH–rate profile shown in the Figure. The profile consists of two straight-line portions of unit slope joined by a bridging region. Rates of disappearance of *S*-(2-aminoethyl)isothiourea,2HBr (Calbiochem) were followed at 235 nm. Replacement of Br^- by the less absorbing BF_4^- did not affect the results. Significant differences in molar extinction coefficients exist at 235 nm where ϵ is 1700 for (I) 500 for (II), and 2900 for (III). When (II) and (III) are produced in equal amounts from (I), no net change in absorption appears and accurate rate constants are difficult to determine in this region near pH 4·2. A solution originally containing (I) displays an increase in absorption below pH 4·2 and a decrease above, demonstrating the transformation from (III) to (II) as the product as the pH increases through the bridging region shown in the Figure. Production of the two products in equimolar amounts occurs near pH 4·2, consistent with the estimate made from the earlier study, performed at more than 200 times greater concentration. Reverse reactions starting with (II) or (III) and even an excess of NH_3 were not detected under the conditions of this study. Hydrolysis to 2-mercaptoethylamine and dicyandiamide does not occur under the conditions used.[1] As indicated by a weak absorption at 265 nm, a minor amount of disulphide formed in some of the final, more basic solutions.

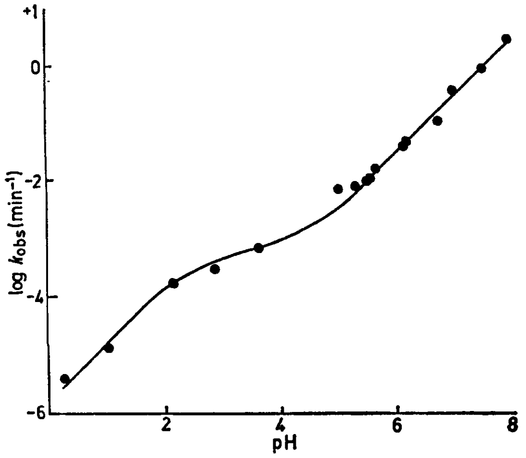


FIGURE. *Logarithm of observed first order rate constants extrapolated to zero buffer concentration in min*$^{-1}$ versus pH *for disappearance of* (I) *at* 25·0° *and* 0·2M *ionic strength controlled with* KCl.

Analysis of the dependence of the reaction rate on buffer concentration reveals that the disappearance of (I) is general base catalysed with respect to free amine(AH^+). For 2-(morpholino)ethanesulphonic acid (IV) buffer (pK_a 6·16) from 0·01—0·20 M concentration, studies at five pH values where the fraction of buffer in the basic form varied from 0·2—0·8 give k_{obs} $(H^+)/(B) = (3{\cdot}6 \pm 0{\cdot}3) \times 10^{-6}$ min^{-1}. Similar values within a factor of 2·5 are obtained for acetic, formic, and chloroacetic acid buffers indicating a low Brønsted exponent in this formulation. This result suggests that hydroxide ion catalysis would not become important until pH > 10. At a given pH, the higher buffer concentrations yield lower final absorbances, indicating that they promote formation of (II) over (III). At a concentration of 0·01 M phosphate buffer is about fifty times more effective as a catalyst than buffer (IV) at pH 6·1—6·7.

The mechanism shown is the simplest that yields a rate expression which accommodates the tripartite pH–rate profile of the Figure and general base catalysis with respect to free amine. By assuming that the tetrahedral carbon addition intermediate, (CH^+), exists in a low, steady-state concentration, we obtain equation (1) for the observed

$$k_{obs} = \frac{K_a k_1}{(H^+)} \times \frac{k_3(H^+) + \Sigma k_4(B)}{k_2 + k_3(H^+) + \Sigma k_4(B)} \quad (1)$$

first order rate constant for disappearance of (I). Due to the rapidity of the reaction at high pH, the acidity constant K_a cannot be measured, but is less than 10^{-8}. The points of the Figure are fitted with the curve of equation (1) drawn with $K_a k_1 = 1{\cdot}6 \times 10^{-6}$ min^{-1}, $k_3/k_2 = 360$ M^{-1}, and $k_4(H_2O)/k_2 = 0{\cdot}020$, where water is the only base of consequence. In the case of buffer (IV) $k_4/k_2 = 2{\cdot}3$ M^{-1}. An alternative formulation with general acid catalysis of a neutral tetrahedral carbon addition intermediate (HB + C) is possible. In either case, the amine expulsion reactions k_2 and k_3 appear to be extremely rapid bond-breaking steps.

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