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METAL ION - BASE CATALYZED REARRANGEMENT OF α-KETOHEMIMERCAPTALS TO α-HYDROXYTHIOLESTERS

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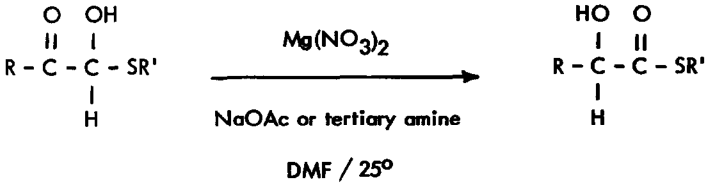
We have observed that α-ketohemimercaptals, formed (2) by equilibrating α-ketoaldehyde monohydrates with thiols (3), rearrange exceedingly slowly in the presence of one equivalent of sodium acetate (180 h) and somewhat faster in the presence of an equivalent of a tertiary amine (4) such as N-methylpyrrolidine (23 h).

However, when magnesium nitrate hexahydrate (0.5 equivalent), or other metal salts (5), was added to these reaction mixtures containing the α-ketohemimercaptal, the rate (6) of rearrangement to the corresponding α-hydroxythiolester was increased by a factor of about 30 and was complete within 7 h in the case of sodium acetate and 0.7 h for N-methylpyrrolidine in isolated yields as high as 95%.



$$R-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}-SR' \xrightarrow[\text{NaOAc or tertiary amine}]{Mg(NO_3)_2} R-\underset{\underset{H}{|}}{\overset{\overset{HO}{|}}{C}}-\overset{\overset{O}{\|}}{C}-SR'$$

DMF / 25°

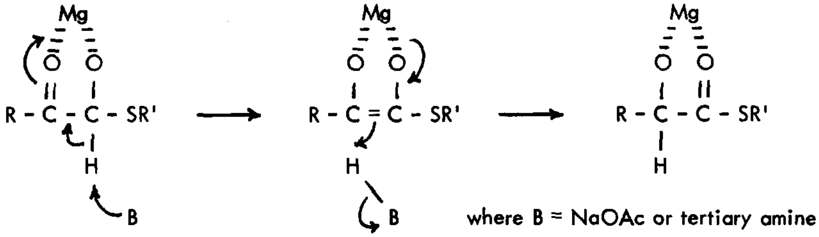
R = methyl, phenyl
R'= butyl, benzyl, furfuryl

The α-ketohemimercaptals and α-hydroxythiolesters were fully characterized by spectroscopic and analytical methods. The most revealing data, using R = methyl and R'= butyl as an example, were as follows: the α-ketohemimercaptal showed strong characteristic bands at 3480 cm^{-1} and 1720 cm^{-1}; and a methyl singlet at 7.68τ and a tertiary hydrogen singlet at 4.75τ. In contrast, the α-hydroxythiolester showed characteristic absorption at 3540 cm^{-1} and 1680^{-1} (7); and a methyl doublet centered at 8.63τ(J = 7Hz) and a tertiary proton quartet centered at 5.74τ (J = 7Hz).

When the reaction was run in DMF-D_2O (75-25%) approximately 80% deuterium (8) was incorporated at the tertiary proton position, as determined by nmr, eliminating the possibility of an intramolecular hydride shift (4a, 9, 10). At this time we suggest the mechanism for this reaction outlined in Scheme I. This mechanism embodies the marked effect of the metal cation on the rate of the reaction, the necessity of base (11), and the incorporation of deuterium.

The pertinence of this study to the glyoxalase I enzyme system (12) will be discussed elsewhere.

SCHEME I



where B = NaOAc or tertiary amine

REFERENCES

1. National Science Foundation Undergraduate Research Participant, Summer 1969.

2. (a) S. Yamazoe, *J. Biochem.(Tokyo)*, 23, 319 (1936); (b) M. Jowett and J. H. Quastel, *Biochem. J.*, 27, 486 (1933); (c) M. P. Shubert, *J. Biol. Chem.*, 111, 671 (1935).

3. Generously supplied by Evans Chemetics, Inc., New York, New York.

4. (a) V. Franzen, *Chem. Ber.*, 88, 1361 (1955); (b) V. Franzen, *ibid.*, 89, 1020 (1956); (c) V. Franzen, *ibid.*, 90, 623 (1957).

5. $AlCl_3$, $CoCl_2$, $FeCl_3$, $FeCl_3 \cdot 6H_2O$, $FeCl_2 \cdot 4H_2O$, $MgCl_2 \cdot 6H_2O$, $MnCl_2 \cdot 4H_2O$, $NiBr_2$, $SnCl_4$, $TiCl_4$, and $ZnBr_2$.

6. The reaction rates at 25° (0.27M in ketoaldehyde and thiol) were: NaOAc $k = 7.1 \times 10^{-6}$ sec^{-1} ($t_{1/2}$ = 28 h), NaOAc / $Mg(NO_3)_2$ $k = 1.8 \times 10^{-4}$ sec^{-1} ($t_{1/2}$ = 1 h); N-methylpyrrolidine $k = 5.6 \times 10^{-5}$ sec^{-1} ($t_{1/2}$ = 3.5 h); and N-methylpyrrolidine /$Mg(NO_3)_2$ $k = 1.8 \times 10^{-3}$ sec^{-1} ($t_{1/2}$ = 0.1 h). Experimental details will be reported later.

7. M. Hauptschein, C. S. Stokes, and E. A. Nodiff, *J. Amer. Chem. Soc.*, 74, 4005 (1952).

8. The incomplete incorporation is probably due to the H_2O present from the metal salt hydrate and α-ketoaldehyde monohydrate.

9. I. A. Rose, *Biochim. Biophys. Acta*, 25, 214 (1957).

10. Control experiments established that neither the α-ketohemimercaptal nor the α-hydroxythiolester incorporate deuterium under the reaction conditions.

11. It should be noted that in the presence of only $Mg(NO_3)_2$, the rearrangement does not occur.

12. K. A. Davis and G. R. Williams, *Biochim. Biophys. Acta*, 113, 393 (1966).