

### Aminolysis of Thioaspirin in Acetonitrile

T. KÖMIVES, A. F. MÁRTON, and F. DUTKA

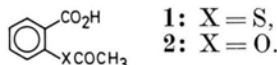
Central Research Institute for Chemistry  
of the Hungarian Academy of Sciences,  
H-1525 Budapest, Hungary

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Neighbouring Group Participation, Thiolester,  
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Reactivity of thioaspirin towards morpholine in acetonitrile approaches that of the "active ester" *p*-nitrophenyl thiolacetate. Insensitivity of the fast reaction to the addition of the strong tertiary nitrogen base triethylamine, as well as the strictly second order kinetics observed strongly suggest that the reactants exist in ion-pair form under the experimental conditions, and that the *o*-CO<sub>2</sub><sup>-</sup> group of thioaspirin acts as an intramolecular general base catalyzed.

During transeptidations catalyzed by cysteine proteinases a thiolester type acyl-enzyme forms<sup>1</sup>. Since the functional groups of these enzymes are located in partly hydrophobic environment<sup>1</sup>, thiolester aminolyses catalyzed by neighbouring acidic and basic groups serve as models for the above processes. To determine the effect of a neighbouring carboxylate (functional group of several cysteine proteinases<sup>1</sup>) on a thiolester aminolysis process we have investigated the reaction of thioaspirin (**1**) with morpholine in acetonitrile<sup>2</sup>.



The aminolysis studied has the following characteristics:

a) The reaction is first order both in ester and in amine. The  $k_{\text{obs}}$  vs [Morpholine] plot is linear with zero intercept (Fig. 1, A).

b) The strong<sup>3</sup> tertiary nitrogen base triethylamine exhibits neither catalytic nor inhibitory effect (Fig. 2, A).

c) **1** is highly sensitive to aminolysis: its reactivity towards morpholine approaches that found for the "active ester" *p*-nitrophenyl thiolacetate<sup>4</sup>.

Thiolester aminolyses in aprotic solvents involve the formation of a zwitterionic intermediate that collapses into products in the rate-limiting step<sup>4</sup>:

Requests for reprints should be sent to Dr. F. DUTKA, Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, Hungary.

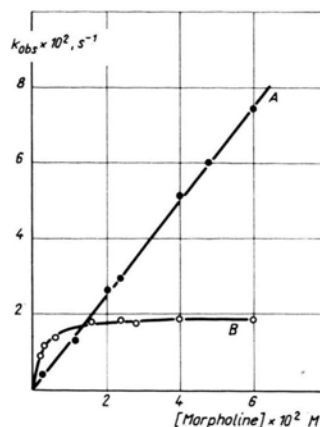


Fig. 1.  $k_{\text{obs}}$  vs [Amine] plot for the reactions of **1** (A) and **2** (B) with morpholine in acetonitrile at 25 °C.

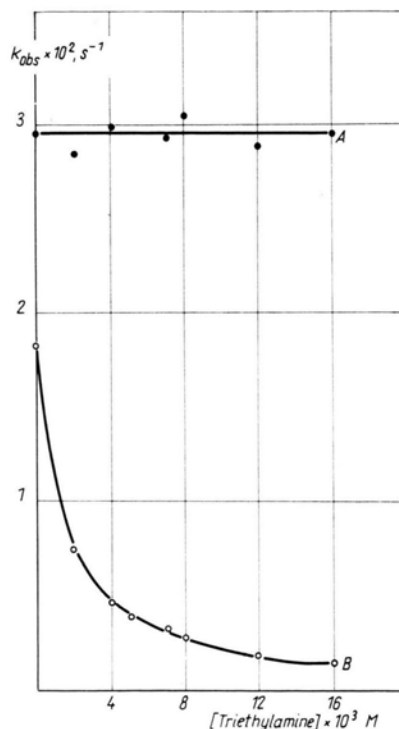
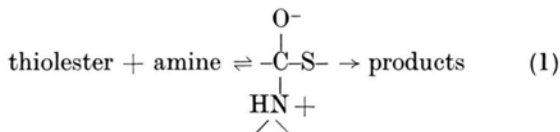


Fig. 2. Effect of added triethylamine on the morpholinolysis of **1** (A) and **2** (B) in acetonitrile at 25 °C ([Morpholine] = 0.024 M).



Introduction of a carboxyl group into the aryl ring of the thiolester molecule leads to an acid-base preequilibrium of Eq. (1), and results in the formation of ion-pair complexes which seems to be general for

carboxylic acid/secondary amine interactions in aprotic solvents<sup>5</sup> (Eq. (2)).



Since the ratio of complexed and free thioaspirin species depends on the amine concentration, linearity of the  $k_{\text{obs}}$  vs [Morpholine] plot (Fig. 1, A) as well as insensitivity of the reaction to the presence of triethylamine strongly suggests that the neutral and anionic species of **1** exhibit similar reactivities towards morpholine.

The  $o$ -CO<sub>2</sub><sup>-</sup> group, however, exerts polar and steric effects impeding the reaction. Thus, the high reactivity of **1** (at least at higher morpholine concentrations and in the presence of triethylamine) can be attributed to intramolecular catalysis by the

$o$ -CO<sub>2</sub><sup>-</sup> substituent. Though our results are in no contradiction with nucleophilic assistance, on the basis of analogous reactions described in the literature<sup>6,7</sup>, we favour a general base participation which facilitates the product-resulting monomolecular decomposition of the tetrahedral intermediate (Eq. (1)) by deprotonation of its ammonium group.

Comparison of the kinetics of the reaction of **1** with that of the oxygen analogue<sup>8</sup> (aspirin (**2**)) reveals that they react *via* different mechanisms. The  $k_{\text{obs}}$  values for the reaction of **2** are higher than those of **1** at [Morpholine]  $< 1.4 \times 10^{-2}$  M (Fig. 1); the reaction of **2** follows MICHAELIS-MENTEN type saturation kinetics (Fig. 1, B) and is inhibited by small amounts of triethylamine (Fig. 2, B). From these facts we assume that **2** reacts according to a mechanism in which a neutral  $o$ -CO<sub>2</sub>H and not an  $o$ -CO<sub>2</sub><sup>-</sup> group participates.

<sup>1</sup> G. LOWE, *Tetrahedron* **32**, 291 [1976].

<sup>2</sup> Reaction rates were measured spectrophotometrically at  $25 \pm 0.05$  °C under the pseudo first order conditions of excess amine. The initial concentration of **1** was  $10^{-4}$  M. Values of the observed rate constants ( $k_{\text{obs}}$ ) were reproducible to  $\pm 4\%$ .

<sup>3</sup> Triethylamine is a stronger base than morpholine in acetonitrile by 1.85 pK<sub>a</sub> units, J. F. COETZEE and G. R. PADMANABHAN, *J. Amer. Chem. Soc.* **87**, 5005 [1965].

<sup>4</sup> T. KÖMIVES, A. F. MÁRTON, and F. DUTKA, *Z. Naturforsch.* **30b**, 138 [1975].

<sup>5</sup> D. F. DETAR and R. W. NOWAK, *J. Amer. Chem. Soc.* **92**, 1361 [1970].

<sup>6</sup> F. M. MENGER, S. WRENN, and H.-S. RHEE, *Bioorg. Chem.* **4**, 194 [1975].

<sup>7</sup> A. J. KIRBY and A. R. FERSHT, *Progr. Bioorg. Chem.* **1**, 1 [1971].

<sup>8</sup> T. KÖMIVES, A. F. MÁRTON, and F. DUTKA, *Chem. Ind.* **1975**, 567.