

An Intramolecular Acyl Transfer Reaction Limited by Substrate Isomerization

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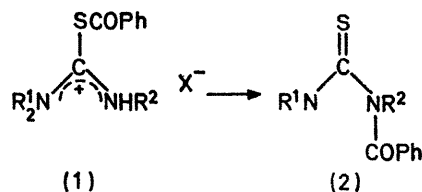
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Summary. The bell-shaped pH-rate profile for the rearrangement of *S*-benzoyl-1,1,3-trimethylisothiuronium bromide to 1-benzoyl-1,3,3-trimethylthiourea has been interpreted in terms of a rate-determining *syn-anti*-isomerization of the sterically favoured but inert species $\text{HA} \rightleftharpoons \text{A}$ to the reactive species $\text{HA}' \rightleftharpoons \text{A}'$.

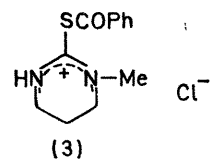
THE interpretation of "bell-shaped" pH-rate profiles is of continuing interest. Once limited in interpretation to the kinetic Scheme 1, which leads to equation (1), it is now

$$k_{\text{obs}} = \frac{k_{\text{rate}} K_{\text{a}_1} a_{\text{H}}}{K_{\text{a}_1} K_{\text{a}_2} + K_{\text{a}_1} a_{\text{H}} + a_{\text{H}}^2} \quad (1)$$

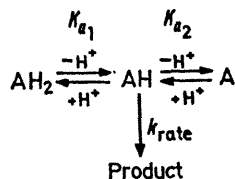
recognized that several other reaction mechanisms provide rate expressions indistinguishable from (1), but in which the values of K_{a_1} and/or K_{a_2} are collections of rate constants and equilibrium constants and in which k_{rate} is not the rate



a; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{X} = \text{Cl}$
 b; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Me}$, $\text{X} = \text{Br}$



constant for the limiting step.¹ Model organic reactions which have bell-shaped pH-rate profiles have been of paramount importance in providing mechanisms which are kinetically indistinguishable from Scheme 1. We report an



SCHEME 1

unusual example of an acyl transfer reaction where the ascending leg of the "bell" is attributed to an acid ionization constant and the descending leg to an acid-dependent isomerization reaction which correctly juxtaposes functional groups for the acyl transfer reaction to proceed. It is suggested that this process serves as a model for enzymatic reactions in which one leg of a bell-shaped pH-profile represents a pH-dependent conformational change at the active site.

S-Acylisothiuronium halides are readily prepared by the reaction of acyl halides with thioureas.² They are converted by treatment with mild base into the corresponding N-acylthioureas. The mechanism of the S → N acyl transfer reactions (1a, b) → (2a, b) is the subject of this communication.

The observed pseudo-first-order rate constants for the disappearance of (1a) and (1b) from aqueous solution (followed spectrophotometrically at 260 nm) were independent of substrate concentration (10^{-5} – 10^{-4} M); the reactions are thus first order in substrate, *i.e.*, the acyl transfer reaction is intramolecular. Plots of logarithms of these rate constants ($\log k_{\text{obs}}$) against pH are shown in the

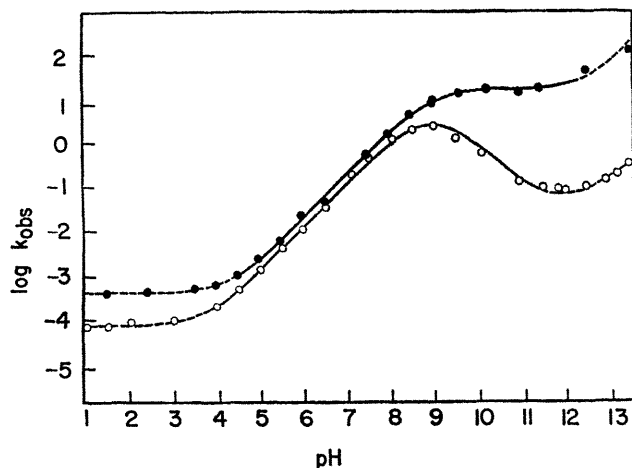
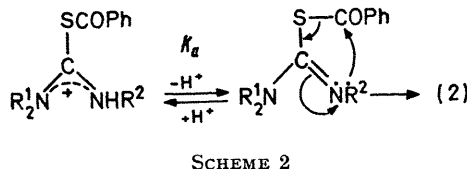


FIGURE. Plots of $\log k_{\text{obs}}$ (k_{obs} in s^{-1}) for the disappearance in aqueous solution (30° , $\mu = 1.0$) of S-benzoylthioureas (1a) (●) and (1b) (○). The points are experimental and the lines theoretical.

Figure. At pH's where the curves are solid the reaction products are (2a) and (2b), and in other regions the products

are those of various hydrolysis reactions; the latter will not be considered further here.

The pH-rate profile for the acyl transfer reaction of (1a) is apparently easily interpretable in terms of Scheme 2.



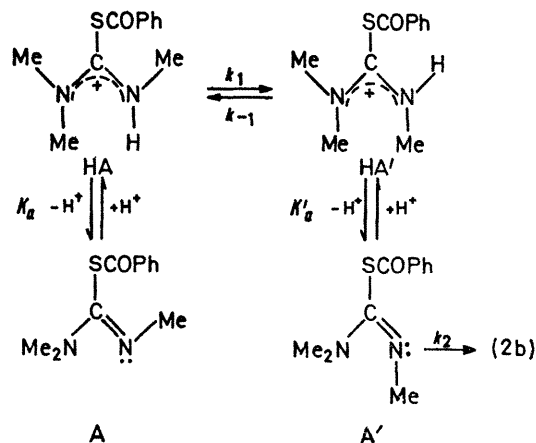
SCHEME 2

With only this simple scheme however, the rate decrease observed with (1b) at high pH is difficult to explain. Rationalizations in terms of a rate-determining breakdown of a protonated tetrahedral intermediate or of formation of an inert hydroxide ion adduct are possible and have been considered but seem chemically implausible especially when it is noted that only 1,1,3-trialkyl substituted compounds exhibit the bell-shaped profile; all less-substituted species, for example (1a), show a simple sigmoid pH-dependence for the acyl transfer reaction.

The bell-shaped profile for (1b) has been interpreted by means of Scheme 3. A steady-state treatment with respect to HA' and A' yields equation (2) which is of the required form.

$$k_{\text{acyl transfer}} = \frac{k_1 k_2 K_a' a_{\text{H}} / k_{-1}}{k_2 K_a K_a' / k_{-1} + (K_a + k_2 K_a' / k_{-1}) a_{\text{H}} + a_{\text{H}}^2} \quad (2)$$

Scheme 3 requires firstly that the reactive species is A'



SCHEME 3

where the lone pair of electrons on the imino nitrogen atom are *syn* to the ester function. Secondly, it is assumed that the predominant species in acid and alkaline solutions are HA and A, respectively. This is not unreasonable because of the intense unfavourable steric interaction between the 1- and 3-methyl groups *anti* to the sulphur in HA' and A' and particularly in the ideally planar cation HA'. This type of steric interaction is believed to account for the anomalous properties of 1,1,3,3-tetramethyl-urea and -thiourea.³ Finally, it is necessary to assume that isomerization by rotation about the (partial) double bond of

the cation is fast compared with isomerization by rotation or inversion in the free base species. Thus the acyl transfer reaction, which must go *via* A', requires the presence of acid to enable isomerization of the predominant A form to A' to occur by way of the protonated species. It is this requirement for acid that leads to the observed rate decrease at high pH.

With lesser substituted derivatives such as (1a) geometric isomers will also be present, of course, but here it is always possible to reach the reactive free base form by way of a series of prototropic equilibria, *i.e.*, it is not necessary specifically to invoke isomerization about a double bond by rotation or inversion prior to the acyl transfer step. Here

then such isomerizations need not become rate-determining to the acyl transfer.

Useful evidence in favour of the rationale outlined above derives from a study of the acyl transfer reaction of the cyclic trisubstituted derivative (3). Here, where isomerization is of course impossible, a sigmoid pH-rate profile is obtained. A precedent to Scheme 3 is seen in the work of Curtin and Miller⁴ who studied the thermal rearrangement of isoimides and suggested the importance of *syn-anti*-isomerization to the observed reaction rates.

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¹ T. C. Bruice and S. J. Benkovic, "Bioorganic Chemistry," Vol. 1, Benjamin, New York, 1966.

² See for example A. E. Dixon and J. Taylor, *J. Chem. Soc.*, 1912, **101**, 2502 and refs. therein to earlier work.

³ M. J. Jansen, *Rec. Trav. chim.*, 1960, **79**, 454, 464.

⁴ D. Y. Curtin and L. L. Miller, *Tetrahedron Letters*, 1965, 1869; *J. Amer. Chem. Soc.*, 1967, **89**, 637.