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Kinetics and mechanism of ring transformation of *S*-[1-(4-methoxyphenyl)pyrrolidin-2-on-3-yl]isothiuronium bromide to 2-methylimino-5-[2-(4-methoxyphenylamino)ethyl]thiazolidin-4-one

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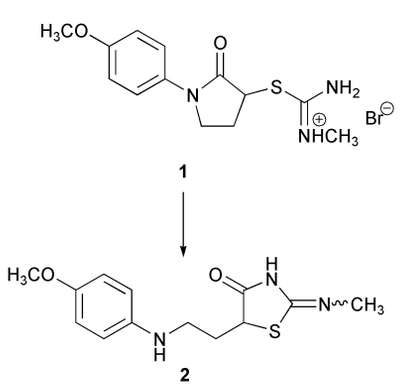
The kinetics and mechanism of transformation reaction of *S*-[1-(4-methoxyphenyl)pyrrolidin-2-one-3-yl]-*N*-methylisothiuronium bromide into 2-methylimino-5-[2-(4-methoxyphenylamino)ethyl)]thiazolidin-4-one have been studied in aqueous solutions of amine buffers (pH 8.1–11.5) and sodium hydroxide solutions (0.005–0.5 mol l^{-1}) at 25 °C and at I = 1 mol l^{-1} at pseudo-first-order reaction conditions. The kinetics observed shows that the transformation reaction is subject to general base, general acid, and hydroxide-ion catalyses. The rate-limiting step of transformation is the splitting-off a proton from the tetrahedral intermediate **In**. The value of pK_a for *S*-[1-(4-methoxyphenyl)-pyrrolidin-2-one-3-yl]-*N*-methylisothiuronium bromide has been determined from the kinetic data (pK_a = 8.75 ± 0.10) and by potentiometric titration (pK_a = 8.90 ± 0.05). With increasing pK_a value of the acid buffer component, the value of Brønsted coefficient β gradually decreases from about 0.7 to almost zero. The value of p$K_a \approx 10$ for the intermediate of base-catalysed transformation has been found from this dependence. In the *N*-methylpyrrolidine and triethylamine buffers, the rate-limiting step of transformation is changed into ring opening of $\mathbf{In}^-$, and the general-base-catalysed reaction changes into a specific-base-catalysed one.

Introduction

Substituted 3-bromo-1-phenylpyrrolidin-2-ones[1] react with substituted thioureas to give the corresponding isothiuronium salts.[2] We have found[2] out that substituted *S*-(1-phenylpyrrolidin-2-on-3-yl)isothiuronium salts in weakly basic media (pH about 9) undergo an intramolecular transformation reaction. In this particular case, the γ-lactam ring is split and a thiazolidine cycle is formed, *i.e.* substituted 2-imino-5-[2-(phenylamino)ethyl]thiazolidin-4-ones are obtained (Scheme 1). The isothiuronium salts having a nitro group in the benzene nucleus undergo a very fast transformation reaction even in solid phase to give the corresponding thiazolidine derivatives.[2] Rearrangements of heterocyclic rings in which a ring is opened and subsequently another ring is closed are of particular interest[3,4] both synthetically and theoretically. Such processes may provide fascinating routes to derivatives that can be obtained only with great difficulties – or not at all – by other procedures. Our system is classifiable[3] as a "classical ring transformation", where the starting and the final systems are of the same size but the heteroatoms and/or their positions have been changed. Ring transformations of five-membered heterocycles dealt with over the recent years were discussed and reviewed.[3–5] The aim of this work is to carry out a detailed study of mechanism of acid-base catalysed transformation reaction of *S*-[1-(4-methoxyphenyl)pyrrolidin-2-one-3-yl]-*N*-methylisothiuronium bromide (**1**) to 2-methylimino-5-[2-(4-methoxyphenylamino)-ethyl]thiazolidin-4-one (**2**).



Scheme 1

Experimental

The kinetic measurements were carried out on an HP UV/VIS Diode Array apparatus in 1 cm closable cells at 25 °C. First a suitable wavelength was chosen for the kinetic measurements on the basis of the spectra scanned from 200 to 1000 nm. Then the cell was always charged with 2 ml aqueous buffer amine solution. After attaining the chosen temperature, 5 μl methanolic solution of the substrate **1** was added so that the resulting substrate concentration would be about 5×10^{-4} mol l^{-1}. The measurements of reactions with half-lives below 2 s (in aqueous triethylamine buffer solutions and aqueous sodium hydroxide solutions) were carried out using a Diode Array Stopped-Flow SX.18 MV-R (Applied Photophysics) apparatus. The observed pseudo-first-order rate constants k_{obs} were calculated from the measured time dependences of absorbance with help of an optimisation program.

The dissociation constant of of isothiuronium salt **1** pK_a = 8.90 ± 0.05 was determined by potentiometric titration of aqueous solution of the substrate (2 ml; c = $5 \cdot 10^{-3}$ mol l^{-1}) using an TITRALAB 3 (Radiometer Copenhagen) apparatus with glass and saturated calomel electrode system at 25 °C. The titration was carried out with 0.1 mol l^{-1} solution of tetrabutylammonium-hydroxide in absolute methanol, and it was

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repeated three times. Benzoic acid was used as the standard ($pK_a = 4.20$).

Results and discussion

The kinetics of transformation reaction of isothiuronium salt **1** to thiazolidine **2** was studied at the conditions of pseudo-first-order, first in aqueous tris(hydroxymethyl)aminomethane (TRIS), morpholine, 2-methoxyethanolamine, ethanolamine, propylamine, butylamine buffers and sodium hydroxide solutions at 25 °C at the ionic strength $I = 1$ mol l^{-1}. The spectral records showed well-developed isosbestic points. The obtained rate constants k_{obs} increased linearly with both the buffer concentration and the basicity of medium (Fig. 1). From the dependences of the rate constants k_{obs} on the concentrations of individual buffer components it follows that the transformation reaction of isothiuronium salt **1** is catalysed by both the OH^- ion and the base and acid buffer components (general acid and general base catalysis).

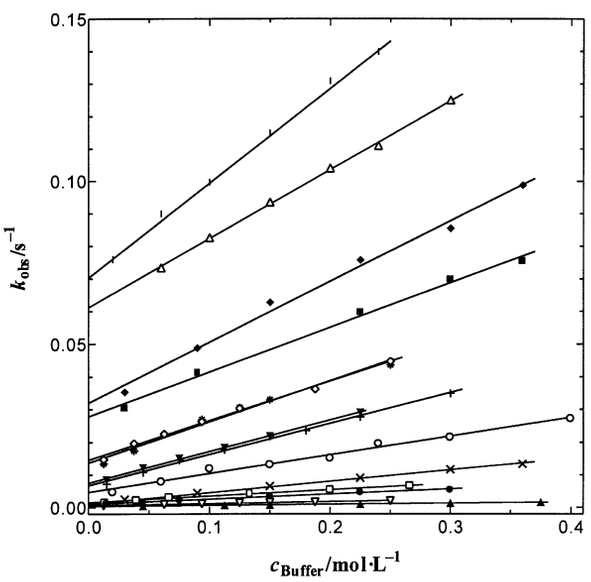
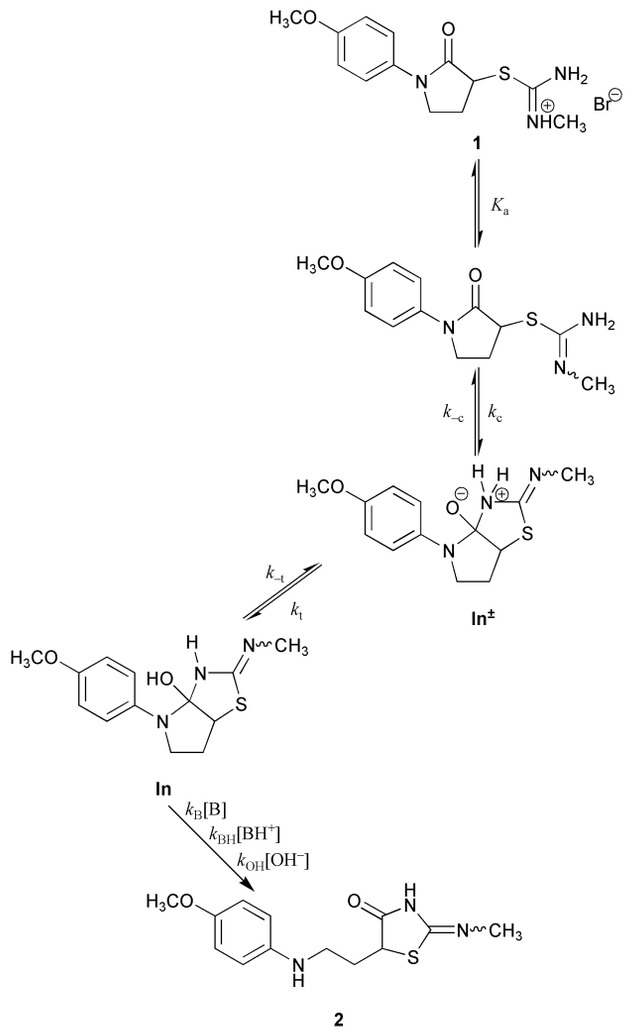


Fig. 1 Dependence of k_{obs} (s^{-1}) on buffer concentration (c_{Buffer}; mol l^{-1}) measured at 25 °C in tris(hydroxymethyl)aminomethane [(1 : 2b) pH = 8.62 (▲), (1 : 4b) pH = 8.95 (▽)], morpholine [(1 : 2b) pH = 9.06 (●), (1 : 3b) pH = 9.24 (□)], methoxyethylamine [(2 : 1a) pH = 9.34 (×), (1 : 1) pH = 9.67 (○), (1 : 2b) pH = 9.99 (+), (1 : 4b) pH = 10.30 (*)], ethanolamine [(1 : 2b) pH = 10.08 (▼), (1:4b) pH = 10.40 (◇)], propylamine [(2 : 1a) pH = 10.56 (◆), (1 : 1) pH = 10.85 (|)] and butylamine buffers [(2 : 1a) pH = 10.58 (■), (1 : 1) pH = 10.91 (△)]. Note: Some buffer ratios are not depicted due to better transparency. (a: acidic; b: basic).

The kinetic dependences found allow one to suggest the following mechanism (Scheme 2) for the transformation reaction. First, a fast pre-equilibrium produces 1-methyl-*S*-[1-(4-methoxyphenyl)pyrrolidin-2-one-3-yl]isothiourea. Then the amino group of free isothiourea intramolecularly attacks the amide carbonyl of pyrrolidine cycle (k_c) to give the bicyclic intermediate $\mathbf{In}^{\pm}$, which can undergo either a very fast proton switch[6–8] between nitrogen and oxygen atom (which proceeds in thermodynamically favourable direction; $k_t \approx 10^6$–10^8 s^{-1}) or a spontaneous very fast decomposition to product **2**. In the case of the fast decomposition of 1-methyl-*S*-[1-(4-methoxyphenyl)-pyrrolidin-2-one-3-yl]isothiourea or the intermediate $\mathbf{In}^{\pm}$ to products, specific catalysis should make itself felt. The intermediate $\mathbf{In}^{\pm}$ can also undergo a general-base- or general-acid-catalysed decomposition similar to that in aminolysis of benzylpenicillin.[9] In such case, however, the found pK_a value of the intermediate would be several units below that found by us. This means that the rate-limiting step of the transformation



Scheme 2

reaction consists in the formation of $\mathbf{In}^-$ from **In**, which is catalysed by OH^- ion, acid buffer component, and base buffer component (Scheme 2).

Figure 2 presents the dependence of log k_{ext} on pH (k_{ext} are values of the observed rate constants extrapolated to zero

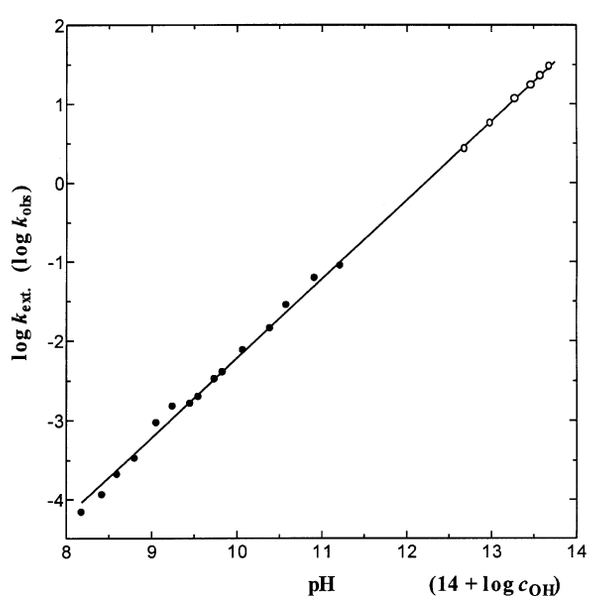


Fig. 2 Dependence of log k_{ext} on pH of individual buffers (●) and dependence of log k_{obs} on (14 + log c_{OH}) (○).

buffer concentration) and the dependence of log k_{obs} on (14 + log c_{OH}) in sodium hydroxide solutions. Both dependences are linear with slope 1.

The overall rate of transformation reaction studied under pseudo-first-order conditions can be expressed by eqn. (1):

$$v = k_{obs}c_s \quad (1)$$

Since the reactive species of the transformation reaction is a free thiourea amino group (the protonated isothiuronium salt undergoes virtually no ring closure), it was necessary to relate the observed rate constant k_{obs} to the concentration of the non-protonated reactive form of isothiourea by dividing k_{obs} through the ratio f = [S]/([S] + [SH$^+$]) calculated from pK_a of isothiuronium salt **1** and pH of the solution according to eqn. (2).

$$k_{cor} = k_{obs}/f = k_{obs}(1 + 10^{(pK_a - pH)}) \quad (2)$$

For this purpose it was necessary to estimate the pK_a value of isothiuronium salt **1**. First, we tried to determine this value by spectral methods. Spectral records of isothiuronium salt **1** in media of various pH values, however, did not show any isosbestic points, and the spectral changes were so small that they were comparable to experimental error. Therefore, we focused our attention on determination of the pK_a by potentiometric titration (see Experimental part). Because the pK_a value of salt **1** is essential part of our kinetic analysis, we additionally estimated it by the kinetic method described below.[10]

At high pH values (butylamine buffers; Fig. 2), practically all substrate should be present in the reactive form of free isothiourea, and at these conditions, the slope of the dependence of log k_{ext} on pH should approach zero; however, this was not observed. In reality, however, the linear dependence is changed but a little (Fig. 2), and the change does not permit any estimation of the pK_a of the salt **1**.

The observed rate constants for the hydroxide-ion-, general-base-, and general-acid-catalysed reactions can be expressed by eqn. (3),

$$k_{obs} = k'_{OH}[OH^-] + k'_B[B] + k'_{BH}[BH] \quad (3)$$

and for the corrected rate constants by eqn. (4)

$$k_{cor} = k_{OH}[OH^-] + k_B[B] + k_{BH}[BH] \quad (4)$$

From eqns. (2)–(4) it is possible to derive a relationship for the constants of base-catalysed recyclisations k_B depending on pK_a of **1** and the pH of medium.

$$k_B = k'_B(1 + 10^{(pK_a - pH)}) \quad (5)$$

The k_B and k'_B values determined for various pH values in morpholine buffers can be used to determine the pK_a value of isothiuronium salt **1** from eqn. (5).

The k_B value was determined from the slopes of dependences of the observed rate constants k_{obs} on concentration of the basic buffer component c_B in basic morpholine buffers 1:5 (pH 9.55) and 1:10 (pH 9.83)

In these pH regions, the substrate is more than 90% in its non-protonated reactive form, and thus the observed rate constants can be expressed by eqn. (6).

$$k_{obs} = \text{konst.} + k_B[B] \quad (6)$$

From Fig. 3 it can be seen that both slopes of the dependences given are practically identical, which means that the k_B value found for the base-catalysed transformation reaction in morpholine buffer is (3.59 ± 0.07) × 10^{-2} l mol^{-1} s^{-1}. Then, using the above-described procedure of pK_a calculation (eqn. (5)), we determined the value of pK_a = 8.75 ± 0.10 for isothiuronium salt **1** which is in good agreement with potentiometric titration.

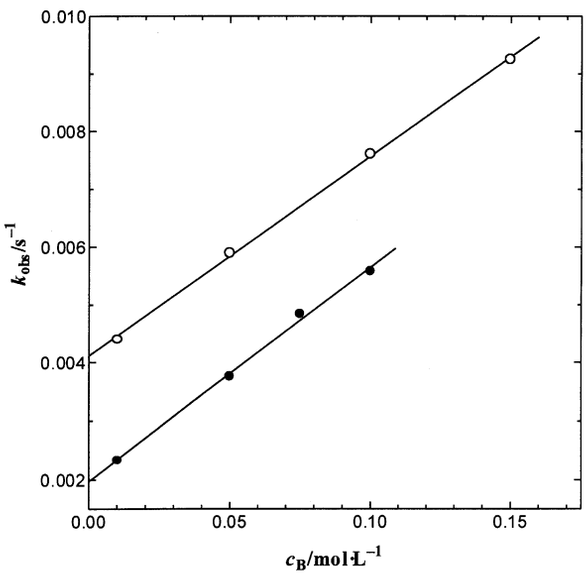


Fig. 3 Dependence of observed rate constant (k_{obs}; s^{-1}) on concentration of basic buffer component (c_B; mol l^{-1}) for the recyclisation reaction **1** ⟶ **2**, ratios [1:5b) pH 9.55 (●)] and [(1:10b) pH 9.83 (○)].

From the determined pK_a value and observed rate constants k_{obs} it was possible to calculate the corrected rate constants k_{cor} for the individual buffers using eqn. (2). These values were plotted against the concentration of the given buffer (morpholine buffer; Fig. 4), and the slope of the linear dependence expressed by eqn. (7) was then used to calculate the corresponding k_{buffer} values. By plotting them against the corresponding ratios c_B/c_{Buffer} (morpholine buffer; Fig. 4 inset) it was in turn possible to obtain linear dependences, expressed by eqn. (9), whose slopes

$$k_{cor} = k'_0 + k_{Buffer}[Buffer] \quad (7)$$

$$k_{Buffer}[Buffer] = k_B[B] + k_{BH}[BH] \quad (8)$$

$$k_{Buffer} = k_{BH} + \frac{(k_B - k_{BH})[B]}{[Buffer]} \quad (9)$$

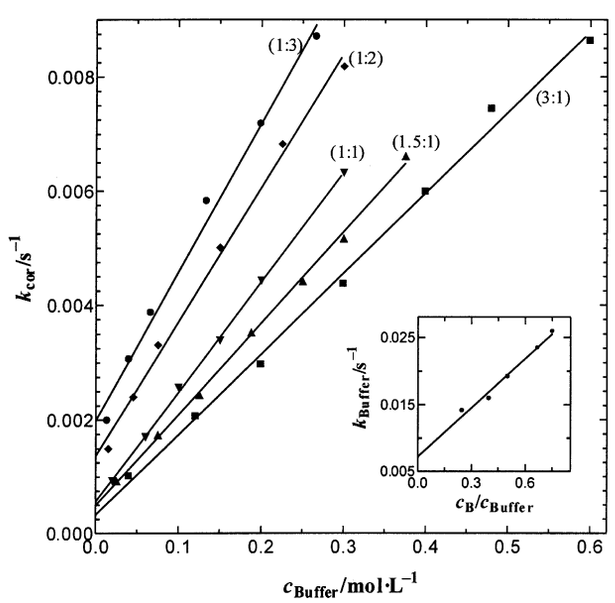


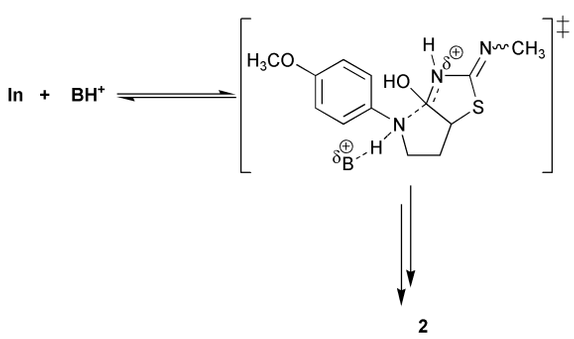
Fig. 4 Dependence of k_{cor} (s^{-1}) on concentration c_{Buffer} (mol l^{-1}) in solutions of morpholine buffers, and k_{buffer} on ratio c_B/c_{Buffer} (inset).

Table 1 Values of catalytic constants k_B, k_{BH} determined in individual buffers, and pK_a values of the protonated amine bases

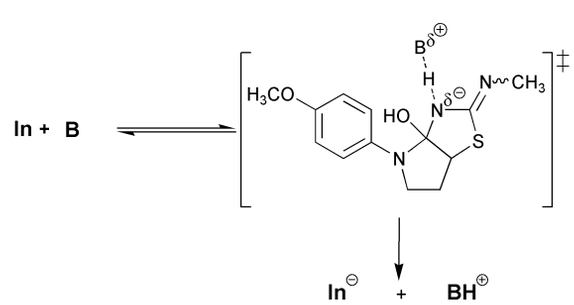
Buffer	pK_a	k_B/l mol^{-1} s^{-1}	k_{BH}/l mol^{-1} s^{-1}
Butylamine	11.38	0.375 ± 0.034	0.021 ± 0.005
Propylamine	10.82	0.351 ± 0.028	0.012 ± 0.006
Ethanolamine	9.68	0.148 ± 0.017	0.008 ± 0.003
Methoxyethylamine	9.45	0.140 ± 0.007	0.002 ± 0.001
Morpholine	8.82	0.036 ± 0.002	0.007 ± 0.001
TRIS	8.10	0.013 ± 0.001	0.002 ± 0.001

gave the difference ($k_B - k_{BH}$) and intercepts gave the values k_{BH}. The whole procedure mentioned is demonstrated on the morpholine buffer; for the other buffers used, the procedure was analogous.

Table 1 presents the individual values of catalytic constants k_B and k_{BH} for the individual buffers along with the pK_a values[7,9,11] of the protonated bases. The general-acid-catalysed transformation of **In** into products (Scheme 3) can be explained similarly to the acid catalysis in the cyclisation of esters of hydantoic acid.[12] In our case, however, proton transfer to the more basic atom of nitrogen, which is adjacent to the benzene ring, as shown in Scheme 3, will be encountered. From Table 1 it is obvious that the general-acid-catalysed transformation reaction proceeds about one order of magnitude more slowly (k_{BH}) than the base-catalysed transformation reaction (k_B) (Scheme 4). The acid catalysis by even weak acids such as protonated ethanolamine, morpholine, or butylamine can make itself felt due to the basicity[6] of the nitrogen adjacent to the benzene ring of **In** (Scheme 3).



Scheme 3



Scheme 4

Moreover, we have found that the course of transformation reaction studied at the same conditions as in the previous cases is quite different from those in *N*-methylpyrrolidine and triethylamine buffers (the ratio of acid and base buffer components was 1 : 1) (Fig. 5). The non-linear increase in the observed rate constant depending on the buffer component can most probably be interpreted by a change in the rate-limiting step of reaction. Similar examples, where the rate-limiting step of proton transfer to base buffer component from oxygen to nitrogen atom is changed, have already been described earlier, *e.g.* in the opening and closure of intramolecular hydrogen bond in 4,6-bis(phenylazo)resorcinol[13] or in the case of ring closure of *N*-(2-methoxycarbonylphenyl)-*N*-methylsulfonamide.[14] At lower pH values (TRIS, morpholine, 2-methoxyethylamine, ethanolamine, propylamine, and butylamine buffers) the rate-limiting step involves the splitting-off of a proton from tetrahedral bicyclic intermediate **In**. In *N*-methylpyrrolidine and triethylamine buffers, the acid-catalysed decomposition of intermediate **In** (k_{BH}) practically no longer makes itself felt. The points in Fig. 5 are values of corrected rate constants k_{cor} calculated from experimental values k_{obs}, and the curve depicts the theoretical course expressed by eqn. (10). This dependence can be explained by the way of transformation of the two intermediates, **In** and **In**$^-$ (Scheme 5).

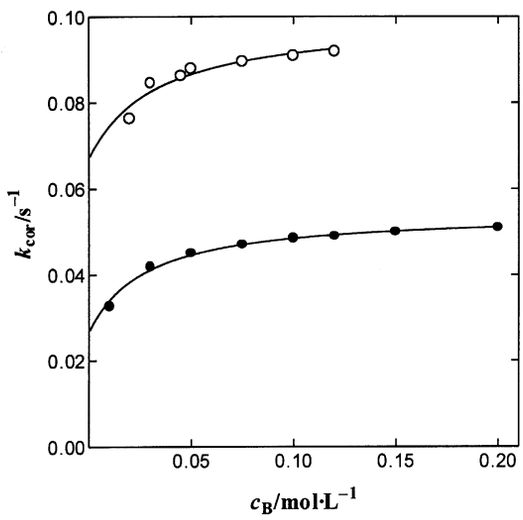
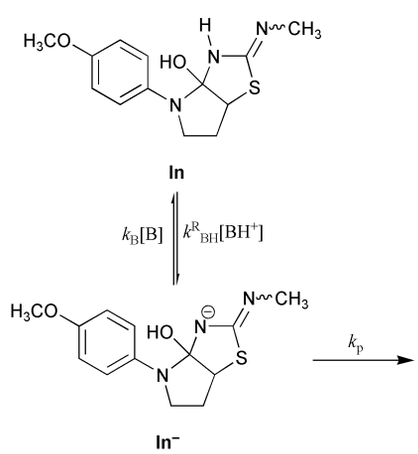


Fig. 5 Dependence of k_{cor} on concentration of basic buffer component (c_B; mol l^{-1}) measured at 25 °C in *N*-methylpyrrolidine buffer (1 : 1) pH 10.51 (●) and triethylamine buffer (1 : 1) pH 11.11 (○).



Scheme 5

The reaction path from **In** to **In**$^-$ predominates at low buffer concentrations (the rate-limiting step is the splitting-off of a proton from the tetrahedral intermediate **In**). At high buffer concentrations, the concentration of acid component is increased and the reverse reaction of the negatively charged intermediate **In**$^-$ to the neutral intermediate **In** starts to be significant (*i.e.* the constant k_{BH}^R becomes significant), and the overall reaction rate ceases to have increasing character (Scheme 5). With increasing concentrations of buffers (Fig. 5) the slope of dependence of observed rate constant of transformation drops. This means that at high buffer concentrations the rate becomes independent of buffer concentration, depending only on the individual pH values of buffers. In a limit case

Table 2 Values of catalytic constants k_B, ratios k^R_{BH}/k_B determined in the individual buffers, and pK_a values of protonated amine bases

Buffer	pK_a	k_B/l mol^{-1} s^{-1}	k^R_{BH}/k_p
Triethylamine	11.08	0.36 ± 0.01	18.37 ± 0.05
N-methylpyrrolidine	10.46	0.24 ± 0.02	6.75 ± 0.06

(a very high concentration of buffer) the catalysis changes from general base catalysis to specific base catalysis, which can be kinetically expressed by means of the Bodenstein steady state approximation for the intermediate **In**$^-$.

The corrected rate constant k_{cor} can, by this approximation, be expressed as in eqn. (10).

$$k_{cor} = k_{OH}[OH^-] + \frac{k_B[B]}{1 + k^R_{BH}[BH]/k_p} \qquad (10)$$

The determined k_{cor} values have been fitted by a curve corresponding to eqn. (10); the intercepts at *y* axis represent the values of products $k_{OH}[OH^-]$, which increase with increasing pH values of the individual buffers in as far as the catalysis by OH^- ion makes itself felt. At higher concentrations of these buffers we can already distinguish specific catalysis.

Table 2 gives the values of base-catalysed decomposition of intermediate **In** (k_B) and the values of ratios k^R_{BH}/k_p, where k^R_{BH} means the acid-catalysed reverse reaction of **In**$^-$ to **In** and k_p refers to the decomposition of **In**$^-$ to products. In triethylamine buffer, the reverse reaction of **In**$^-$ to **In** is about 18 times as fast as the decomposition of **In**$^-$ to products, whereas in *N*-methylpyrrolidine buffer the respective factor is only about 7.

From the Brønsted dependence of log k_B on pK_a (Fig. 6) it follows that the value of Brønsted coefficient β gradually decreases from about 0.7 to almost zero, which means that the proton transfer from the intermediate **In** to a basic buffer component B gradually becomes more favourable thermodynamically. From the dependence it was possible to estimate (by the graphical method[6] or method of stepwise approximation[15]) the value 10.1 for the pK_a of the intermediate **In** (Fig. 6).

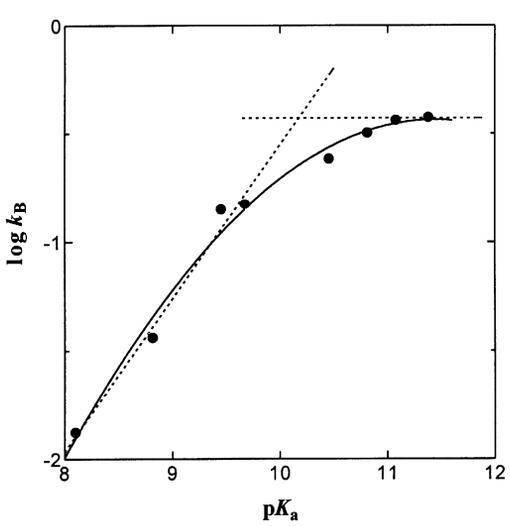


Fig. 6 Brønsted dependence of k_B on pK_a of protonated amine bases.

The kinetics of transformation reaction was also measured in solutions of sodium hydroxide (at the concentrations of 0.005–0.5 mol l^{-1}). From the dependence of observed rate constant on concentration of sodium hydroxide (Fig. 7) it follows that the water-catalysed transformation reaction is practically insignificant ($k_0 = 0$). From this dependence (Fig. 7) we have determined the value of $k_{OH} = (60.9 \pm 0.6)$ l mol^{-1} s^{-1}, which is practically identical with the values ($k_{OH} = (60 \pm 10)$ l mol^{-1} s^{-1}) found in the individual amine buffers.

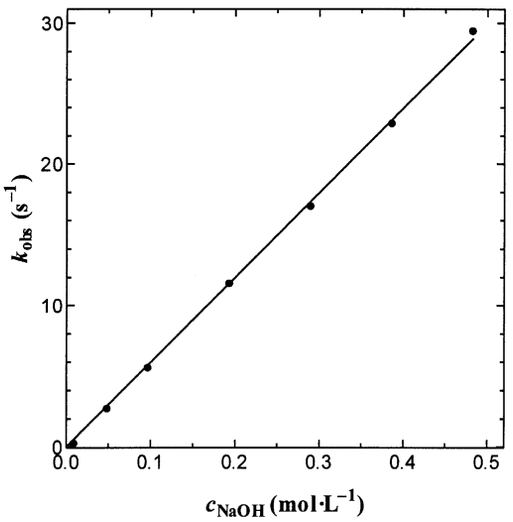


Fig. 7 Dependence of observed rate constant k_{obs} upon concentration of sodium hydroxide for the recyclisation reaction **1** ⟶ **2** at 25 °C and at $I = 1$ mol l^{-1}.

Conclusions

The transformation reaction of *S*-[1-(4-methoxyphenyl)-pyrrolidin-2-one-3-yl]-*N*-methylisothiuronium bromide into 2-methylimino-5-[2-(4-methoxyphenylamino)ethyl)]thiazolidin-4-one proceeds by several reaction pathways, being catalysed by both basic and acidic buffer components. The base-catalysed transformation is about ten times as slow as the acid-catalysed reaction. The bicyclic **In**, whose p$K_a \approx 10$, decomposes in the rate-limiting step. In tertiary amine buffers, a change in the rate-limiting step takes place: the decomposition of **In**$^-$ gradually becomes rate limiting, and the reaction changes into a specific-base-catalysed one. A further kinetic study of the transformation reaction of an analogous derivative, carrying a further methyl group, *viz.* at the nitrogen atom of amino group that attacks the amide carbonyl group, is expected to provide further insight into the mechanism of this transformation reaction and make it more precise.

Acknowledgements

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