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MECHANISM OF CRISS-CROSS REACTION OF AROMATIC GLYOXALIMINES WITH POTASSIUM CYANATE AND THIOCYANATE‡

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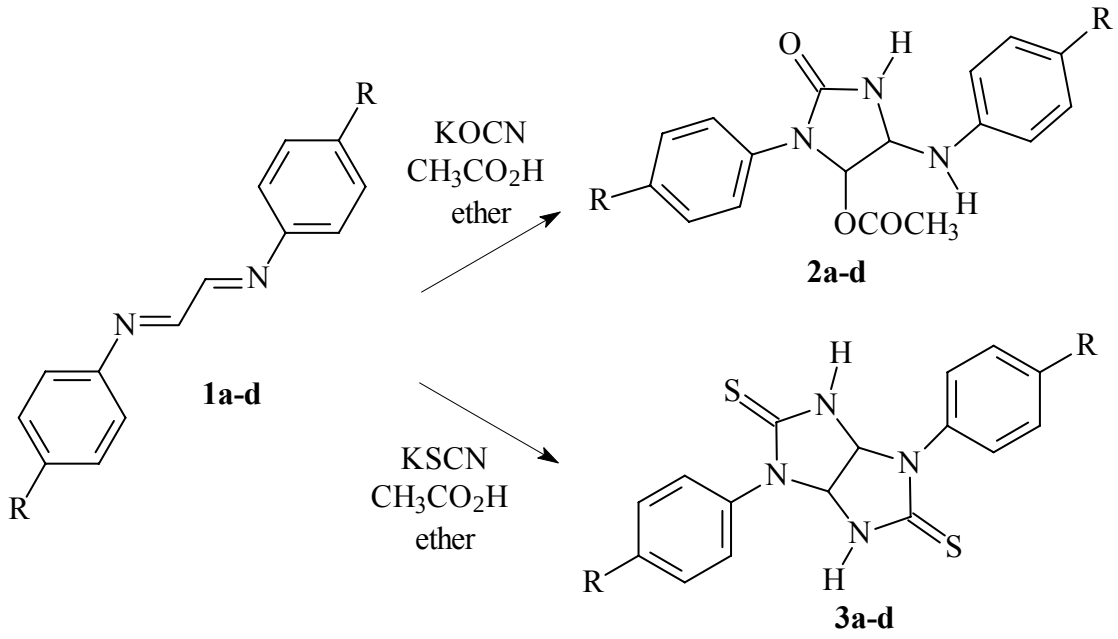
Abstract – Aromatic 1,4-diazabuta-1,3-dienes (glyoxalimines) react with potassium cyanate and thiocyanate in ethereal acetic acid to give the corresponding4-acetoxy-5-(4-substituted phenylamino)-3-(4-substituted phenyl)-imidazolidin-2-ones and perhydroimidazo[4,5-*d*]imidazol-2,5-dithiones, respectively. In order to learn more about the reaction mechanism, kinetic measurements have been carried out. It was found that the reaction involves a direct nucleophilic addition of thiocyanate anion to 1,4-diazabuta-1,3-diene, whereas the less nucleophilic cyanate anion requires acid catalysis.

INTRODUCTION

Criss-cross cycloaddition reactions[1] represent a special type of 1,3-dipolar cycloaddition reactions. Their first case, reported as long ago as 1917, was the reaction of 2,3-diazabuta-1,3-dienes (azines) with phenyl isocyanate and with potassium cyanate or thiocyanate in acetic acid medium.[2] Later on also acyl isocyanates,[3] sulphonylisocyanates,[4] maleinimides[5] and acrylates[6] were used as dipolarophiles. Moreover, the criss-cross cycloaddition was extended to the reactions of 1,2-diazabuta-1,3-dienes[7] and 1,4-diazabuta-1,3-dienes[8-11] with various dipolarophiles. Although these reactions with HOCN and HSCN have been known for 90 years, their mechanism has not yet been dealt with in any kinetic study.

The aim of this work is to study the substituent effect on kinetics and mechanism of reaction of 1,4-diazabuta-1,3-dienes (**1a-d**) with potassium cyanate and thiocyanate in glacial acetic acid to give

corresponding 4-acetoxy-5-(4-substituted phenylamino)-3-(4-substituted phenyl)imidazolidin-2-ones (**2a-d**) and perhydroimidazo[4,5-*d*]imidazol-2,5-dithiones (**3a-d**) (Scheme 1).



	a	b	c	d
R	4-OCH_3	4-CH_3	4-F	4-Cl

Scheme 1

RESULTS AND DISCUSSION

The reaction kinetics of 4-substituted 1,4-diazabuta-1,3-dienes (**1a-d**) with potassium cyanate or thiocyanate was studied in a mixture of glacial acetic acid and diethyl ether (1:1) at the pseudo-first-order conditions. The concentration of **1a-d** was always $5 \cdot 10^{-5}$ mol·l^{-1} and that of KOCN or KSCN was in the range of 0.01-0.1 mol·l^{-1}. The pseudo-first-order reaction conditions offer the advantage of avoiding any significant interference caused by consecutive reactions that complicate the synthesis. The yields of preparation[11] of **3a-d** are about 65-70%.

It was found that in both the reactions with KOCN and with KSCN the observed rate constant k_{obs} increases (with all the substituents at the benzene nucleus of **1a-d**) linearly with the concentration of KOCN or KSCN (Figure 1), which means that the reaction order with regard to KXCN (X = O, S) is equal to 1, and the transition state of the rate-limiting step involves two molecules (bimolecular reaction). Hence, this finding excludes the possibility of trimolecular reaction going through a bicyclic transition state as suggested[9] by *Takahashi* and *Miyadai*.

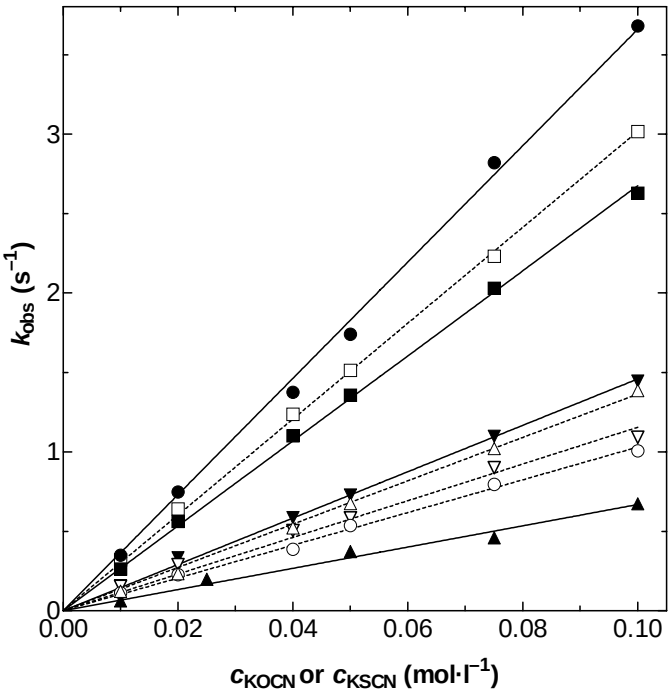


Figure 1 – Dependence of the observed rate constants k_{obs} (s^{-1}) on the concentration of potassium cyanate c_{KOCN} (mol·l^{-1}) and potassium thiocyanate c_{KSCN} (mol·l^{-1}) for formation of **2a** (Δ), **2b** (□), **2c** (∇), **2d** (○), **3a** (▲), **3b** (■), **3c** (▼), **3d** (●) at 25 °C.

Table 1 – Values of bimolecular rate constants

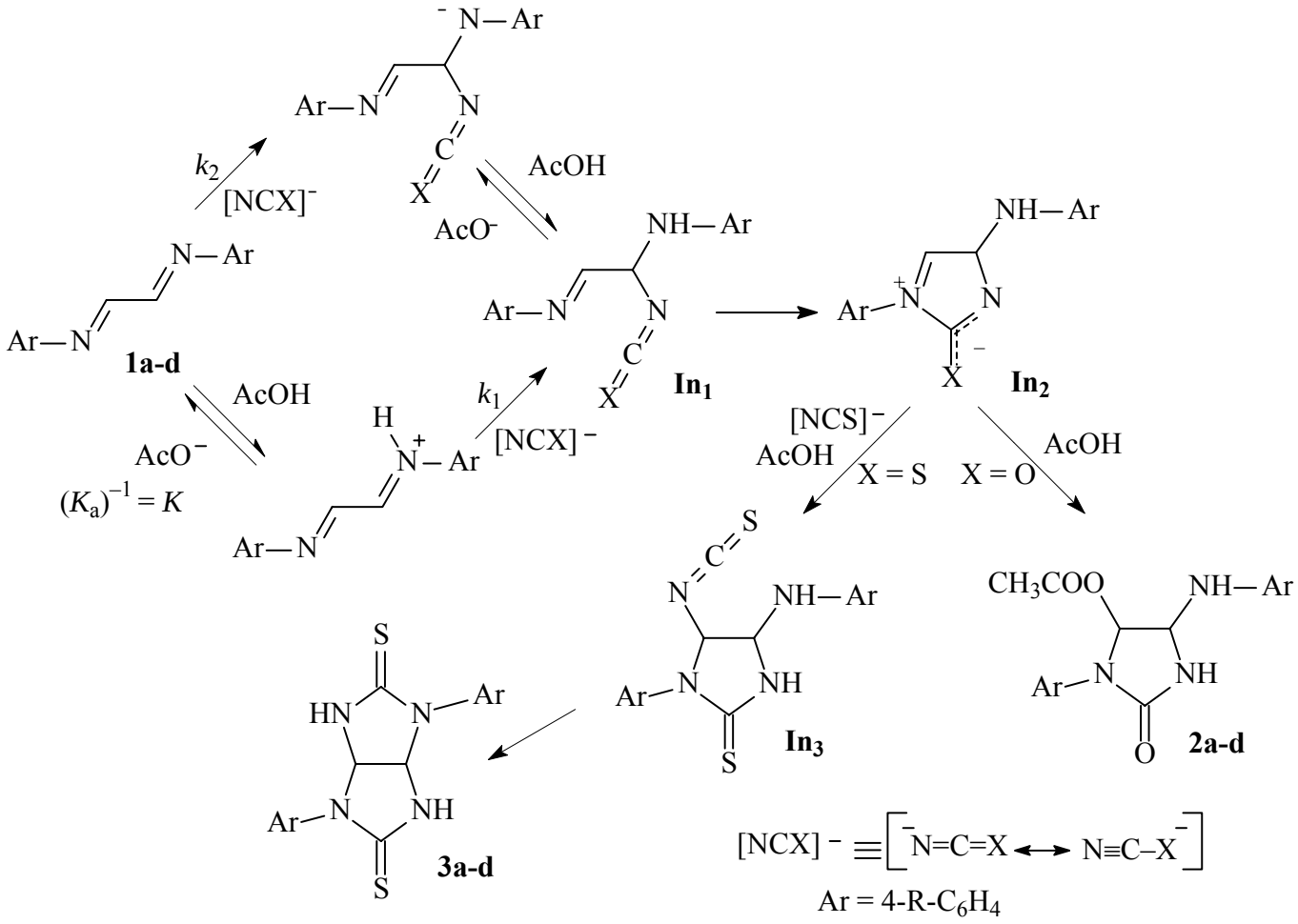
	2a	**2b**	**2c**	**2d**	**3a**	**3b**	**3c**	**3d**
k' (l·mol·s^{-1})	13.6±0.2	30.2±0.2	11.5±0.5	10.3±0.2	6.7±0.2	26.7±0.2	14.6±0.1	36.6±0.5

Furthermore, it was found that neither alkyl nor aryl isocyanates/isothiocyanates react with **1a-d** at similar conditions. Although literature[2] reports that the reaction of isomeric benzaldazines[2] with alkyl isocyanates takes place, nevertheless, it is only achieved in a sealed tube at 150 °C. In this case a likely mechanism consists in the imine nitrogen acting as a nucleophile that adds[1] to isocyanate group. In the case of **1a-d**, the imine nitrogen (due to the electron acceptor effect of aromatic ring) is much less nucleophilic than in the case of benzaldazines, being incapable of attacking the isocyanate/isothiocyanate group. Comparison of dissociation constants of thiocyanic acid (pK_a = –1.28, water)[12] and acetic acid (pK_a = 4.74, water)[13] also indicates that in the reaction mixture used there is almost no non-dissociated thiocyanic acid (or its tautomeric form – isothiocyanic acid) present. In the case of the less acidic cyanic acid (pK_a = 3.7, water)[14] its relative content is higher but, nevertheless, it does not exceed 10% of total analytical concentration. All these facts indicate that the reaction is of ionic nature, the thiocyanate/cyanate ions behave towards **1a-d** as nucleophiles.

The nucleophilicity of $[SCN]^-$ is very high (n_{MeI} = 6.70), being comparable[15] with that of CH_3O^- (n_{MeI} = 6.29) or that of N_2H_4 (n_{MeI} = 6.61) and much higher than that of CH_3COO^- (n_{MeI} = 4.30), whose concentration, moreover, is negligible due to the low value of dissociation constant. Both thiocyanate and

cyanate anions are ambident nucleophiles. The negative charge is predominantly localised at the sulphur atom in thiocyanate anion,[16] whereas in cyanate anion its position is at the nitrogen atom.[16] The literature[17] reports that in the reaction of methyl 3,5-dihydroxybenzoate with $[SCN]^-$ the ratio of product formed by the attack of methyl group by sulphur atom to that formed by the attack by nitrogen atom is 24:1, but in carbonyl compounds there takes place either direct[18] attack by nitrogen atom or a rapid isomerisation[18] of primary acyl thiocyanate into isothiocyanate. Similar behaviour can also be presumed in the reaction of $[SCN]^-$ with imines. The nucleophilic addition could also be positively affected by the acid catalysis that makes itself felt in the protonation of **1a-d** by acetic acid. The position of this acid-base equilibrium is again determined by pK_a(**1a-d**) and pK_a of acetic acid. The literature[19,20] presents the pK_a values of imines of the type Ar–N=CH–Ar in the range of 2-3 depending on the substitution at the aromatic nuclei. The values of pK_a(**1a-d**) should be similar or even lower, which means that the relative abundance of protonated imine is low.

The nucleophile $[XCN]^-$ is added to the imine and/or its protonated form, which is much more reactive than carbonyl group.[21] In analogous way, the protonated imine reacts also with such weak nucleophile as is water,[22] or the free imine reacts with hydroxide ion.[23] In our case it was found that even the glyoxalimine (**1a**) itself undergoes slow hydrolysis by action of the traces of water present in the medium used (i.e. Et_2O + AcOH 1:1) (k_{hyd}(**1a**) = $4.62 \cdot 10^{-3}$ s^{-1}). However, the reaction in the presence of $[XCN]^-$ is faster by more than two orders of magnitude. The addition of $[XCN]^-$ to **1a-d** produces intermediate **In$_1$**, which then undergoes intramolecular cyclisation reaction giving the five-membered intermediate **In$_2$**. Since the reaction is first order with regard to $[XCN]^-$, the rate-limiting step probably involves **In$_1$** formation. Although the imine nitrogen in intermediate **In$_1$** is little nucleophilic (due to the delocalisation of free electron pair from nitrogen into the adjacent benzene nucleus), the ring closure giving the favourable five-membered cycle is easy thanks to high effective molarity[24] caused by sterical proximity (the proximity effect). An analogous attack by imine nitrogen was also suggested in the case of intermolecular reaction of 2,4-diphenyl-1,3-diazabuta-1,3-dienes with alkyl and aryl isothiocyanates.[25] The intermediate **In$_2$** produced is rapidly protonated by acetic acid (whose molar concentration is ca 2 orders of magnitude higher than that of KSCN), which is followed by the attack by another $[SCN]^-$ anion or acetate ion. Cyanate anion $[OCN]^-$ is four orders of magnitude weaker nucleophile (n_{MeI} = 2.73)[26] than thiocyanate anion, and its nucleophilicity is even lower than that of acetate ion (Scheme 2). Therefore, instead of a criss-cross product analogous to **3a-d** the reaction predominantly produces **2a-d**. A similar mechanism presuming a nucleophilic addition of $[SCN]^-$ to imine grouping was also suggested in the paper[9] in which the reagent used was trimethylsilyl isothiocyanate, whose Si–N bond is relatively weak.



Scheme 2

Kinetic equation (1) holds true if the reaction goes by the path involving a fast pre-protonation of **1a-d**:

$$k_{obs} = \frac{k_1 \cdot K \cdot [H^+] \cdot [XCN^-]}{1 + K \cdot [H^+]} \qquad (1)$$

As the starting amine is protonated to a very small extent only, the term $K \cdot [H^+] << 1$, and Eq. (1) changes into Eq. (2). The equilibrium concentration of the proton is the same in all the measurements, hence it can be involved in the rate constant k'.

$$k_{obs} = k_1 \cdot K \cdot [H^+] \cdot [XCN^-] = k' \cdot [XCN^-] \qquad (2)$$

The values of bimolecular rate constants k' (Table 1) obtained as slopes ($k_1 \cdot K \cdot [H^+]$) of dependences presented in Figure 1 show that electron-acceptor substituents accelerate the reaction with KSCN, but they slow down the reaction with KOCN. In both series a deviating point belongs to the 4-CH_3 derivative

1b, which is probably due to its different character – in contrast to OCH_3, Cl and F, methyl group possesses no free electron pairs capable of direct conjugation with the reaction centre. Glyoxalimines carrying electron withdrawing groups (such as NO_2, CN, CH_3CO, but also H) cannot be prepared,[11] and that is why the *Hammett* correlation can only be constructed from a small number of points. An estimate of reaction constant ρ for the reaction of derivatives **1a**, **1c** and **1d** with KSCN is about +1, while that of the reaction with KOCN is about –0.2.

For the mechanism involving fast pre-protonation (Scheme 2), the value of reaction constant ρ is given by the sum of reaction constant of this pre-protonation (ρ_1) and that of the nucleophilic attack (ρ_2). The value of ρ_1 for dissociation of iminium salts[20] is ρ = 1.5; hence, the equilibrium viewed in opposite direction has $\rho_1 = -1.5$. The value of ρ_2 should be positive and of smaller absolute magnitude. Hence, the sum $\rho_1 + \rho_2$ should have a relatively small negative value. This is reflected by the reaction constant found for the reactions of **1a-d** with KOCN. However, for the reactions of **1a-d** with KSCN the value of ρ is positive, which means that another reaction path has to be considered. The thiocyanate anion, as compared with the cyanate anion (n_{MeI} = 2.73),[26] is four orders of magnitude more nucleophilic, and thus it is capable of nucleophilic addition reaction also with the non-protonated imine. On the presumption that this addition is the rate-limiting step of the whole sequence, the process is described by the kinetic equation (3) where the protonation equilibrium constant is missing:

$$k_{obs} = k_2 \cdot [SCN^-] \qquad (3)$$

In such case, the observed reaction constant ρ only reflects the attack of substrate by thiocyanate ion, and its positive value (ρ = +1) is in accordance with the attack taking place at the second atom from the nucleus.

Hence, in conclusion it can be stated that the reaction of 1,4-diazabuta-1,3-dienes (**1a-d**) with potassium cyanate or thiocyanate in ethereal acetic acid probably proceeds by the ionic mechanism in which the cyanate/thiocynate ions behave towards **1a-d** as nucleophiles. The thiocyanate anion, being a strong nucleophile, is able to be added even to non-protonated substrate, while the less nucleophilic cyanate anion requires acid catalysis. The lower nucleophilicity of cyanate ion is also the reason why the reaction does not give a bicyclic product analogous to **3a-d**.

EXPERIMENTAL

The reaction was followed spectrophotometrically using Applied Photophysics SX.18MV-R Stopped Flow Reaction Analyser under pseudo-first-order conditions (c(**1a-d**) = $5 \cdot 10^{-5}$ mol·l^{-1}; c(KXCN) =

0.01-0.1 mol·l^{-1}) at 25 °C. The stock solutions of **1a-d** were prepared in dry ether and injected into the reaction cell (in a ratio of 1:1) together with fresh stock solution of KNCO or KNCS in glacial acetic acid (p.a.; min. 99.8%). The absorbance-time (*A*-*t*) dependences were measured at 380 nm. The observed pseudo-first-order rate constants k_{obs} were calculated from these dependences with the help of an optimisation program using Eq. (4).

$$A - A_0 = (A_\infty - A_0)(1 - e^{k_{obs}t}) \qquad (4)$$

In all the kinetic runs the standard deviation in the fit was always less than 1.5% of the quoted value, being usually between 0.2 % and 0.4 % of the quoted value. Each measurement was repeated five times.

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