^{15}N NMR study of the mechanism of the reaction of amidoximes with nitriles in the presence of $ZnCl_2$ and HCl

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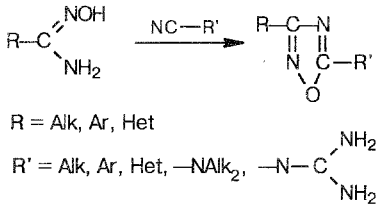
The structures of complexes formed during the transformation of amidoximes into 1,2,4-oxadiazoles by the action of nitriles in the presence of zinc chloride and HCl were studied by ^{15}N NMR spectroscopy.

Key words: ^{15}N NMR, 1,2,4-oxadiazoles, amidoximes, nitriles.

We have previously developed a new general method for the synthesis of 1,2,4-oxadiazoles by treatment of carbonitriles with amidoximes in the presence of zinc chloride and HCl.[1] The method makes it possible to synthesize diverse derivatives of 1,2,4-oxadiazoles, including amino- and guanidino-1,2,4-oxadiazoles.[2,3]

Scheme 1



In the present work aimed at the investigation of the reaction mechanism, we studied the reaction of chloroacetamidoxime (**1**) with chloroacetonitrile (**2**) enriched with the ^{15}N isotope (Scheme 2).

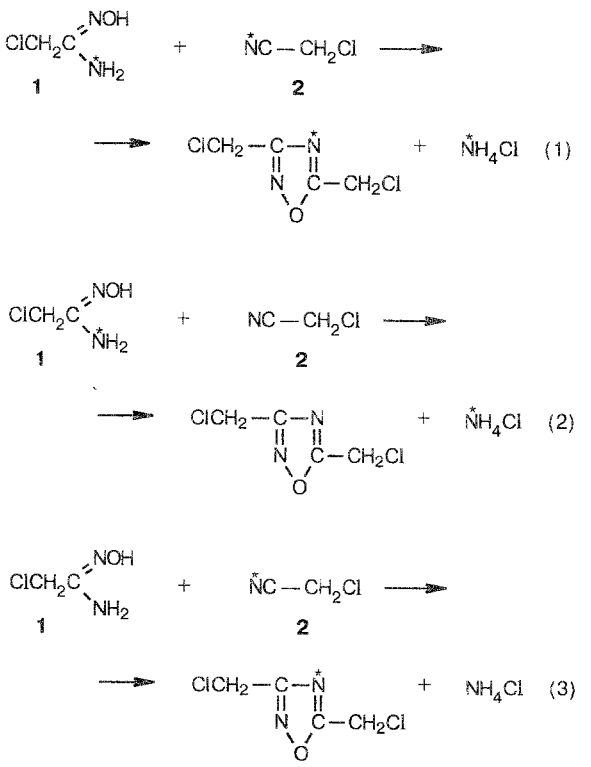
To bind all of the amidoxime in a complex, excess $ZnCl_2$ and nitrile were used.

We recorded the ^{15}N NMR spectra of the starting compounds and mixtures of them (in which at least one component contained a NH_2 or CN group labeled with ^{15}N) with zinc chloride and HCl in butyl acetate.

It was found that the addition of zinc chloride to a solution of a labeled amidoxime in butyl acetate results in a downfield shift of the signal of the ^{15}N atom of the amidoxime group (δ −294.94; $^1J_{NH}$ = 91.1 Hz) by 28.1 ppm relative to the original value of the chemical shift (CS) for the amidoxime (δ −323). In our opinion, this implies that the amidoxime forms a complex with zinc chloride, in which the amino group of the amidoxime moiety is involved in the metal coordination environment. It is known that amidoximes readily form complexes with various metal salts including zinc chloride, but their structures have not been studied.

It may be assumed based on the literature data[4] that zinc chloride binds with the two nitrogen atoms in amidoxime **1** to form complex **A** (Scheme 3). The hydroxide group remains intact in the complex formed and participates in the subsequent reaction step.

Scheme 2



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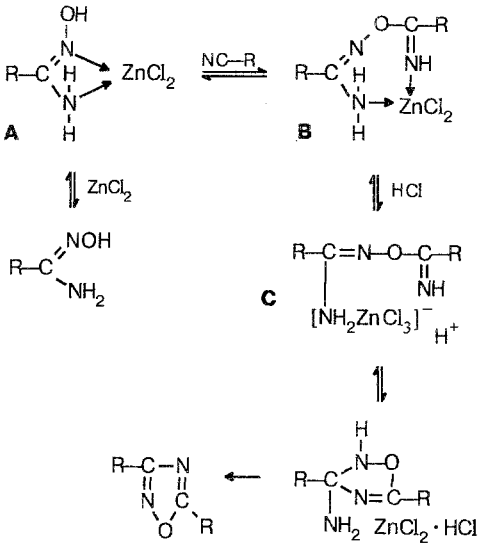
After the addition of an excess of the nitrile enriched with the ^{15}N isotope to a solution of labeled amidoxime and zinc chloride in butyl acetate (Scheme 2, Eq. 1), the spectrum displays, apart from a signal of the nitrile nitrogen atom in the region −128.22 ppm (t, $^2J_{NH}$ = 2.0 Hz), a doublet signal with a chemical shift −206.34 ppm ($^1J_{NH}$ = 78.0 ppm) and a triplet signal with a chemical shift −293.93 ppm (J_{NH} = 96.0 ppm). The signals were assigned based on the data for mixtures containing a nonlabeled amidoxime and a nonlabeled nitrile. If a ^{15}N-nonlabeled nitrile is added to a solution of a labeled amidoxime and zinc chloride, the spectrum does not contain a doublet signal but only contains a triplet with a chemical shift −293.93 ppm. If nonlabeled amidoxime and labeled nitrile are taken, the spectrum only contains a signal of the nitrogen atom in the starting nitrile and a doublet with a chemical shift −206.34 ppm.

Hence, the triplet signal refers to the nitrogen atom of the amidoxime group, while the doublet refers to the nitrogen atom of the moiety formed from the nitrile. Probably, the addition of the nitrile to the hydroxyl group of the amidoxime occurs to give complex **B**.

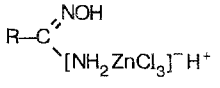
When hydrogen chloride is passed through a solution containing the labeled amidoxime, nitrile, and zinc chloride, the spectrum shape changes, *viz.*, two broadened singlets are observed: one with a CS of −184.2 ppm and the other with a CS of −298.5 ppm ($W_{1/2}$ = 20—40 Hz).* If unlabeled nitrile is used, then the signal at −184.2 ppm is absent, while if the amidoxime is not labeled, the signal at −298.5 ppm disappears. Thus, the latter signal refers to the nitrogen atom of the amino group in the amidoxime moiety, while the former signal refers to the nitrogen atom of the moiety formed from nitrile. Both signals are broadened, which evidently indicates that a rapid proton exchange between the nitrogen atoms of these moieties occurs. When the temperature of a solution containing the labeled amidoxime, nitrile, zinc chloride, and HCl is decreased to −50 °C, both signals broaden greatly. When the mixture is heated at 60 °C for 1.5 h, the signals disappear, and a singlet appears at −146.87 ppm which corresponds to the ^{15}N atom in the oxadiazole ring. It should be noted that cyclization involves the abstraction of the imino group of amidoxime **1**. One of the possible explanations as to why two broadened signals appear in the spectrum is that the introduction of HCl results in the replacement of the amino group from the coordination environment of zinc by a chlorine atom followed by the transformation of complex **B** into complex **C**. The exchange of a proton between the imino group and the amino group of the amidoxime moiety occurs in the latter complex. It should be emphasized that the passage of HCl through a concentrated solution containing an amidoxime, a nitrile, and zinc chloride results in the precipitation of a product, whose elemental composition corresponds to a complex consisting of the amidoxime, the nitrile, zinc chloride, and HCl in the molar ratio 1 : 1 : 1 : 1. When this compound is heated in butyl acetate, the corresponding oxadiazole is formed.

Scheme 3



Thus, based on the ^{15}N NMR spectroscopic data, the following scheme of the formation of intermediate complexes during the synthesis of 1,2,4-oxadiazoles and nitriles in the presence of zinc chloride and HCl can be suggested (Scheme 3).

As follows from Scheme 3, the reagents should be added in a definite sequence in order for the process to occur successfully. First, a nitrile should be added to a mixture of an amidoxime and zinc chloride in butyl acetate. Then, after the formation of the corresponding complex **B**, HCl should be added. Otherwise, if the amidoxime is added to a mixture consisting of nitrile, HCl, and zinc chloride, or the nitrile is added to the mixture containing the nitrile, zinc chloride, and HCl, the yields of 1,2,4-oxadiazoles decrease, since the formation of complexes **B** and **C** is hindered in this case. Probably, this hindrance results from the formation of a type **D** complex incorporating an amidoxime, zinc chloride, and HCl. One can believe that this complex cannot react with a nitrile at room temperature because of deactivation of the oxime group of the amidoxime fragment due to the electron-withdrawing effect of the remaining part of the complex.



D

* The spectrum also contains four triplet signals. Two of them (with chemical shifts of −244.8 and −246.38 ppm) are analogous to the signals appearing when HCl is passed through a solution containing a nitrile and zinc chloride. The remaining two signals have chemical shifts of −245.74 and −250.55 ppm. These signals do not disappear after heating the reaction mixture and therefore do not relate to the complexes studied.

Complex **D** can undergo destruction when heated. However, this would be accompanied by nitrile polymerization, decreasing the yield of the 1,2,4-oxadiazole.

It turned out that the optimum sequence of mixing (see above) of chloroacetamidoxime with an equimolar amount of cyanoguanidine results in the corresponding 1,2,4-oxadiazole in a yield twice as high as in the other cases. In fact, the yield of 3,5-di(chloromethyl)-1,2,4-oxadiazole was 64 % with the optimum sequence of reagent mixing, while when the variant with the formation of complex **D** was used, the yield decreased to 34—40 %.

Thus, assumptions about the reaction mechanism were made based on the study performed, which allowed us to optimize the conditions of the synthesis of 1,2,4-oxadiazoles.

Experimental

^{15}N NMR spectra were recorded on a Bruker AM-300 spectrometer with a working frequency of 3042 MHz. The chemical shifts are given relative to $CH_3{}^{15}NO_2$ as the external reference (the upfield chemical shifts are given with a "minus" sign). The ^{15}N NMR spectra were obtained with and without proton decoupling, as well as in the INEPT mode. The ^{15}N chemical shifts were measured to within ±0.05 ppm, while the ^{15}N—^{1}H coupling constant is 0.5±0.05 Hz.

The labeled amidoxime and nitrile were obtained by the procedure reported in Ref. 1.

The molar reagent ratio in the solutions was always amidoxime : nitrile : zinc chloride : hydrogen chloride = 1 : 1 : 4 : 1.

Prior to use, butyl acetate was dried with $MgSO_4$ and distilled.

Preparation of 3,5-di(chloromethyl)-1,2,4-oxadiazole. ***a.*** $ZnCl_2$ (5 g, 3.68 mmol) and chloroacetonitrile (5 g, 3.68 mmol) were added to a suspension of chloroacetamidoxime (1.0 g, 0.92 mmol) in butyl acetate (8 mL). The reaction mixture was stirred until a homogeneous solution formed, then HCl (0.34 g, 0.92 mmol) was passed through it. The mixture was kept at 20 °C for 20 min and heated for 30 min at 120—125 °C. The reaction mixture was cooled to ~20 °C and washed with water (10 mL). The aqueous layer was extracted with ether (4×5 mL). The organic layers were combined and dried with $MgSO_4$. The solvent was distilled off, and the residue was distilled *in vacuo* to give 0.98 g (64 %) of 3,5-di(chloromethyl)-1,2,4-oxadiazole, b.p. 68 °C (1 Torr), *cf.* Ref. 1: 68 °C (1 Torr). The mass spectrum is identical to that reported previously.[1]

b. $ZnCl_2$ (5 g, 3.68 mmol) was added to a solution of chloroacetonitrile (5 g, 3.68 mmol) in butyl acetate (8 mL), and the reaction mixture was stirred until a homogeneous solution formed. Chloroacetamidoxime (1.0 g, 0.92 mmol) was added to the reaction mixture, which was then stirred until the formation of a homogeneous solution and treated as in the above procedure. The yield of 3,5-di(chloromethyl)-1,2,4-oxadiazole was 35 %.

c. $ZnCl_2$ (5 g, 3.68 mmol) was added to a suspension of chloroacetamidoxime (1.0 g, 0.92 mmol) in butyl acetate (8 mL). The reaction mixture was stirred until the formation of a homogeneous solution, then HCl (0.34 g, 0.92 mmol) was passed through it. Chloroacetonitrile (5 g, 3.68 mmol) was added, and the reaction mixture was treated as described above. The yield of 3,5-di(chloromethyl)-1,2,4-oxadiazole was 39 %.

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