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Solid state and dynamic solution structures of *O*-carbamidine amidoximes gives further insight into the mechanism of zinc(II)-mediated generation of 1,2,4-oxadiazoles

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ABSTRACT

Three new iminium salts $[H_2N{=}C(R)ON{=}C(R')NH_2](p\text{-}TolSO_3)\cdot\frac{1}{2}H_2O$ ($[\mathbf{1}{-}\mathbf{3}](p\text{-}TolSO_3)\cdot\frac{1}{2}H_2O$; R/R′ = $NMe_2/PhCH_2$ **1**, $NMe_2/p\text{-}BrC_6H_4$ **2**, $N(CH_2)_5/p\text{-}BrC_6H_4$ **3**) were synthesized via Zn^{II}-mediated amidoxime-cyanamide coupling and their solid structures were studied by X-ray diffraction. Solution structure and conformational changes of $[\mathbf{1}{-}\mathbf{3}](p\text{-}TolSO_3)\cdot\frac{1}{2}H_2O$ were studied by dynamic NMR. The obtained quantitative data were supported by DFT calculations. All the obtained results help to understand the relative stability of the salts $[H_2N{=}C(R)ON{=}C(R')NH_2](X)$ (R = $NAlk_2$, Alk, Ar) and give a further insight into the mechanism of Zn^{II}-mediated generation of 1,2,4-oxadiazoles. The electron delocalization and sesquialteral bonds in the $[H_2N{=}C(NR_2)ON{=}C(R')NH_2]^+$ system was recognized by estimation of values of activation energy barriers (14–18 kcal/mol by DNMR and 16–17 kcal/mol by DFT calculations) for the rotation around the CN bonds for the NR_2 groups and inspection of the solid-state X-ray data along with the Wiberg bond indices (intermediate single/double bond order for the CN distances). This electron delocalization is responsible for the stabilization of the positively charged iminium cation. The moderate strength hydrogen bonding between the oxime *N* atom and the $=NH_2$ group, which is verified from the X-ray, DNMR experiments, and by using quantum chemical calculations, stabilizes the iminium salt, but it is still weak to prevent the heterocyclization. Theoretical calculations of the heterocyclization of $[H_2N{=}C(R)ON{=}C(R')NH_2]^+$ to 1,2,4-oxadiazoles demonstrated that it is kinetically hindered to a greater extent for R = $NAlk_2$ and this explains their lower reactivity as compared to the iminium salts with R = Alk, Ar.

1. Introduction

It is commonly accepted that imines RR′C=NR″ represent a class of highly reactive species and in the overwhelming majority of cases undergo various types of secondary redox and non-redox transformations regardless of the donor substituents R/R′/R″. Such is the reactivity of some RR′C=NR″ imines they are often dubbed *elusive*. We [1,2] and other groups [3–6] have demonstrated explicitly that highly reactive RR′C=NH are stabilized substantially by a number of metal centers. Following coordination these compounds can be stored intact in the coordinated form under normal conditions for an extended period. It appears moreover that the formation of imines is a critical step driving many metal-involving reactions, e.g. condensation of NH_3 ligands with ketones [5,7], reduction of oximes [8], oxidative dehydration of amine species [9,10], and nucleophilic addition to ligated RCNs [2–4,11,12]. The intriguing combination of inertness in the metal-bound form with the high reactivity in the metal-free form of RR′C=NH imines suggests a wealth of unexplored practical applications [13–17].

Being interested in the chemistry of reactive imines [13–16], we studied the addition of amidoximes [11,12,18–20] and simple oximes [21–28] to RCN ligands (Scheme 1, route *a*) that leads to a relatively little explored class of imino derivatives, viz. HN=C(R)ON=CR′R″ (R = Alk, Ar, $NAlk_2$; R′ = Alk, Ar; R″ = H, NH_2, Alk, Ar) (for reviews see Refs. [2,29–31]; for recent works see Refs. [11,18]).

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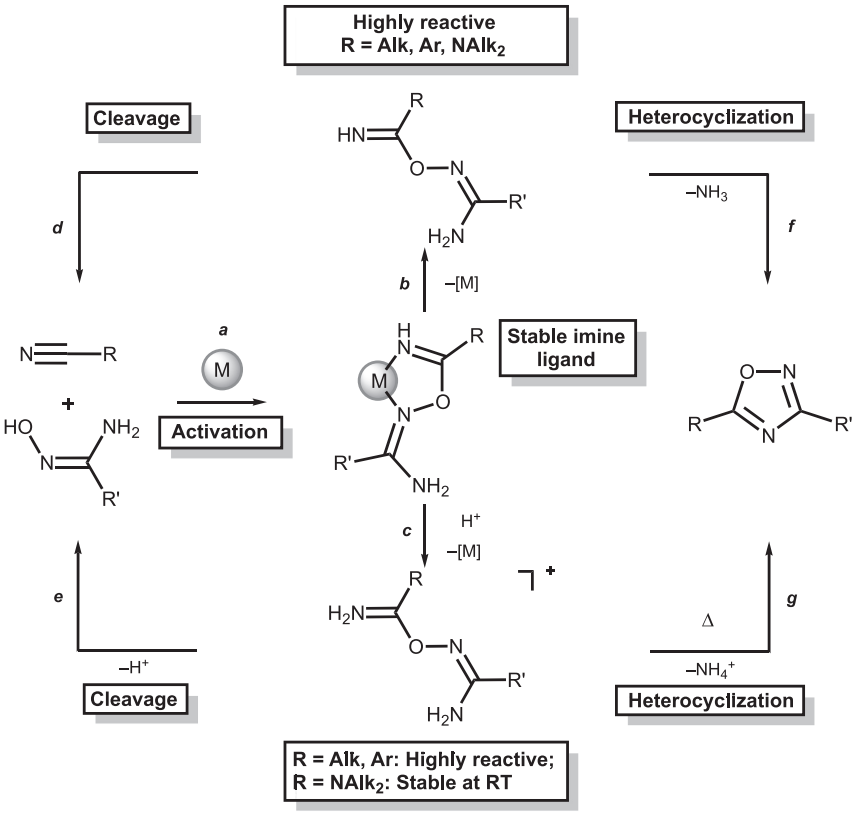

Scheme 1. Transformations of O-imidoyl amidoximes and their salts.

These stable metal-bound imines upon decoordination (route *b*) readily split to the parent nitrile RCN and oxime R′R″C═NOH [18,23] (R′/R″ = Alk, Ar; route *d*) or undergo heterocyclization [18] (for R′ = NH_2; route *f*). In metal-free organic chemistry, all attempts to stabilize these imines by, for instance, introducing fluoroalkyl groups in RCN′s, failed insofar as the treatment of Alk_FCN with R′R″C═NOH [R′/R″ = Me/Me, Ph/NH_2, *p*-HONC(NH_2)C_6H_4/NH_2, *p*-HONC(NH_2)C_6H_4/N(CH_2)$_4$, *p*-HONC(NH_2)C_6H_4/N(CH_2)$_5$] leads to an equilibrium mixture of the imine HN═C(Alk_F)ON═CR′R″ with the parent Alk_FCN and R′R″C═NOH [32]. All reactions described in this paragraph indicate that imines HN═C(R)ON═CR′R″ are perfectly stabilized by ligation to a metal center, but they are virtually elusive in the metal-free form.

Within our project on reactions of metal-activated substrates bearing CN group (for reviews see Refs. [2,29–31]), we recently studied the Zn^{II}-mediated coupling between RCN′s (R = Alk, Ar, NR_2) and the amidoximes HON═C(R′)NH_2 (R′ = Me, Ph) furnishing the chelates [$ZnCl_2${HN═C(R)ON═C(R′)NH_2}] (route *a*) [11]. The chelated ligands are stable but quite reactive being decoordinated (routes *b*–*d* and *b*–*f*) [18]. However, we found that the imine species with R = NR_2 by sharp contrast to those with R = Alk and Ar, could be trapped (route *c*) and isolated as the stable salts [H_2N═C(NR_2)ON═C(R′)NH_2](*p*-$TolSO_3$) upon treatment of the zinc(II) chelates with *p*-$TolSO_3H$ [11]. Most likely H^+ takes the role of the metal center, displace the zinc(II) center, and blocks the electron pair of the HN═ functionality thus preventing the imine from further transformations; delocalization of the positive charge additionally stabilizes this compound.

Taking into account that imines HN═C(R)ON═C(R′)NH_2 and their salts (routes *f* and *g*) serve as useful precursors for facile generation of 1,2,4-oxadiazoles [11,18,32] having a broad spectrum of various applications in biology and medicine [33–38], we thought that the study of the solid state and solution structures of persistent [H_2N═C(R)ON═C(R′)NH_2](*p*-$TolSO_3$) salts warranty investigation. In accord with our plan, we synthesized new [H_2N═C(R)ON═C(R′)NH_2](*p*-$TolSO_3$) (R/R′ = NMe_2/$PhCH_2$ **1**, NMe_2/*p*-BrC_6H_4 **2**, N(CH_2)$_5$/*p*-BrC_6H_4 **3**) species, studied their X-ray molecular structures and verified hydrogen bonding by combined X-ray crystallographic and theoretical methods. In addition, we studied solution structure and conformational changes of the [H_2N═C(R)ON═C(R′)NH_2](*p*-$TolSO_3$) species by dynamic NMR and the obtained quantitative data were supported by DFT calculations. We also performed theoretical calculations of the heterocyclization of the iminium salts [H_2N═C(R)ON═C(C_6H_4Br-*p*)NH_2](X) (R = Et, Ph, NMe_2) to 1,2,4-oxadiazoles, that is the main route of transformation of these salts in a solution. All the obtained results give a further insight into the mechanism of Zn^{II}-mediated generation of 1,2,4-oxadiazoles [11,18,39–41] and results are consistently disclosed in paragraphs that follow.

2. Experimental

2.1. Materials and instrumentation

Solvents were obtained from commercial sources and used as received. The amidoximes RC(═NOH)NH_2 (R = *p*-BrC_6H_4, $PhCH_2$) were synthesized according to the literature methods [11]. Melting points were measured on a Stuart SMP30 apparatus in capillaries and were not corrected. Microanalyses were carried out on a Euro EA3028-HT analyzer. Electrospray ionization mass-spectra were obtained on a Bruker micrOTOF spectrometer equipped with an electrospray ionization (ESI) source. The instrument was operated both in positive and in negative ion mode using a *m*/*z* range 50–3000. The capillary voltage of the ion source was set at −4500 V