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(*Z*), not (*E*) – an end to a century of confusion about the double bond stereoisomers of 3-amino-2-cyano acrylates

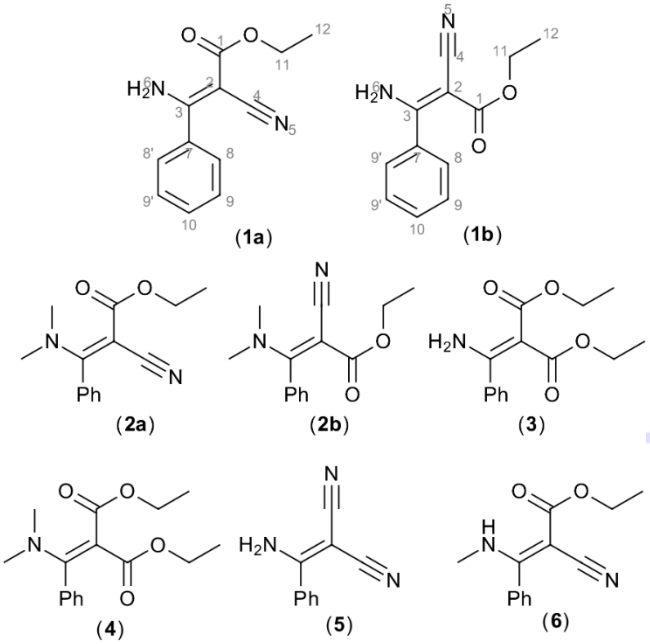
Søren S. Donau, Matthias Bechmann, Norbert Müller, Thorbjørn T. Nielsen, Reinhard Wimmer*

Abstract: Potent and selective myosin inhibitors are of vast scientific interest in the development of treatments for diseases involving myosin dysfunction or overactivity. A novel fungicide, Ethyl 2-cyano-3-amino-3-phenylacrylate (commercialized as “Phenamacril”), was recently identified as an inhibitor of myosin-5 in *F. graminearum*. Although the compound has been known since 1900, a general confusion concerning the stereochemical configuration at the exocyclic double bond persists in the literature, thus restricting further drug development of this compound and derivatives. Using NMR and quantum mechanical calculations, this work establishes the stereoconfiguration as always being the (*Z*)-form and that the effect of a single hydrogen bond is crucial in keeping these types of molecules in a single configuration.

Introduction

Ethyl 2-cyano-3-amino-3-phenylacrylate has been known since 1900,[1–3] but it was not until the end 1990´s that the antifungal properties of this compound were recognized and patented under the develop-code *JS399-19.*[4,5] Since 2004 several scientific papers have dealt with the anti-fungal properties of the compound[4–30] and recently the compound has been commercialized as a fungicide under the trade name *Phenamacril*. In 2015 myosin-5 was identified as a target protein of Phenamacril.[23] Myosin inhibitors have a vast medical potential[31] and have been investigated as therapeutical drugs for cancer.[31,32] Obviously, knowledge of the correct structure is a prerequisite for any potential drug development and pharmacophore modeling.

Although the compound has been known for almost a century prior to the discovery of its antifungal and myosin inhibiting properties, vagueness and general discrepancy regarding the double bond configuration appears in the published literature (see ESI† S2 - S4 for a complete overview of the structures and naming of the compound found in peer-reviewed articles, patents and websites). Excluding non-peer reviewed literature, only few of the fungicide-related studies of Phenamacril have sketched the molecular structure.[5,23,24,29] Additionally, to the best of our knowledge, none of the peer-reviewed fungal activity related papers include the double bond configuration in the IUPAC-name of the compound, nor do they provide any data upon the double bond configuration of the active fungicide. Judging from the existing drawings of the molecular structure represented in fungi related literature there is a vast overrepresentation of the (*E*)-configuration[5,23,24,29] (**1b**, Scheme 1), seemingly making the (*E*)-isomer the most widely accepted stereoisomer of Phenamacril.



Scheme 1. Structures mentioned in the text: Phenamacril is shown both in its *Z* (**1a**) and *E* (**1b**) form. The same goes for *N,N*-dimethyl Phenamacril (**2a** and **2b**). All compounds except 1b were produced synthetically. Structure verification, NMR spectra and their assignments are given in the ESI S8 – S19

Other 3-amino cyanoacrylates with various degrees of structural similarity to Phenamacril have been investigated for their anti-tumor,[33] antivirus[34] and herbicide[35–40] activities. In these studies using X-ray single crystal diffraction (XRD) to investigate the configuration of the compounds one commonly finds the predominance of the isomer where the amine and the ester moiety are positioned *cis,*[33,36–40] with only two exceptions for compounds containing a large and bulky N-substituent.[34,35] From the XRD experiments an intramolecular hydrogen bond between the amino and the ester moiety was also derived and its formation was thought to be the main reason for the predominance of the specific stereoconfiguration.[33,36,37]

The structures found in the above-mentioned studies differ from the otherwise sketched *(E)*-isomer in the studies of Phenamacril and the most complete information on the structure of

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† Electronic Supporting Information (ESI) for this article (overview of published Phenamacril structures, experimental methods, NMR and MS data and DFT-calculations) is given via a link at the end of the document.

Phenamacril, is found in non-fungicide related literature.[41–43] Studies of Phenamacril[42] and the closely related methyl ester derivative,[41] revealed that the stereochemical configuration of these compounds were independent of the configuration of the starting materials as only a single stereoisomer was observed for the product.[41,42]

Albeit not being completely conclusive, Morel and co-workers deduce the compound to be in the (*Z*)-configuration, as the IR- and NMR-data exhibited hydrogen bonding of the amino proton ascribed to the ester moiety. However, the line of argumentation for the hydrogen bond of the amino proton connecting to the ester and not the nitrile, was not clearly described.[41] Similarly, Jalander and Lönnqvist,[42] reported the stereochemical configuration to be *Z* (**1a**). However, this conclusion was based on a weak evidence, the absence of an NOE between the ethyl- and the phenyl- hydrogen atoms in 2D ^{1}H NOESY. While the findings of Jalander and Lönnqvist do point towards the *Z*-isomer, which would fit to the studies of other 3-amino cyanoacrylates, a complete verification of the structure has still not been provided. A more recent study from 2014,[43] synthesized compound **1a** as a precursor for a *N-chloroimine* compound and, while the (*Z*)-configuration is given in both the molecular drawing and the IUPAC name, the paper only includes ^{1}H-NMR data and does not touch upon how the configuration was derived.

For a range of compounds containing enamine moieties, interconversion between diastereomeric forms has been shown to take place in liquid state or solution under different conditions.[44–49] For these compounds, the ability to rotate around the partial double bond depends on the substituents of the amine[44] and the alkene.[47] A correlation between the ability to form intramolecular hydrogen bonds and the predominance of one isomer has been observed in several studies.[44–46] Introducing further complexity, some compounds even crystallize in only one isomeric form, while an equilibrium between the isomeric forms exists in liquid state or solution,[44] excluding solid state methods as a means to determine the stereochemistry of aminocyanoacrylates in solution.

Results and Discussion

The 1D ^{1}H- and ^{13}C-spectra of Phenamacril (Figure 1 (i)) show only one set of signals suggesting that either (i) only one isomeric form is present, or (ii) fast interconversion between the two isomeric forms occurs under the experimental conditions, hence the measured NMR-signals are averaged between the two isomers. It is highly unlikely that both isomers should be present without dynamic interconversion, as one would expect these to exhibit signals at different chemical shifts for several of the hydrogens and carbons.

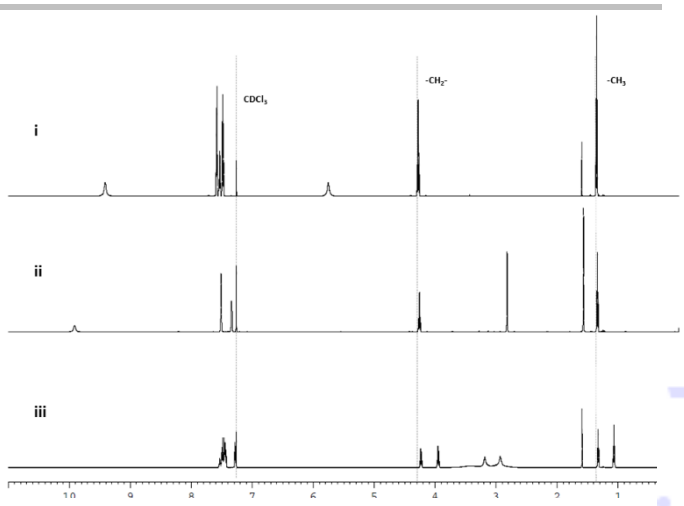

Figure 1. ^{1}H-spectra of (i) **1a**, (ii) **6** and (iii) a mixture of **2a**, **2b**. Ethyl group resonances of Phenamacril and the solvent peak are marked by vertical dashed lines through the spectra.

The ^{1}H-NMR spectrum for Phenamacril shows two distinct broad signals at 9.41 ppm and 5.75 ppm (in $CDCl_3$). These signals were unambiguously assigned to the amino protons. Changing the solvent from $CDCl_3$ to DMSO-d6, one observes a significant (5.75 to 8.91 ppm) deshielding of one amino proton, but not the other one(9.41 to 9.23 ppm).

Deshielding indicates formation of intermolecular hydrogen bonds with the solvent. Additionally, data from several ^{1}H-NMR spectra recorded at different concentrations of Phenamacril in $CDCl_3$, showed no significant changes in the chemical shifts of the amino protons (data not shown). Altogether, these observations consistently indicate that the high chemical shift of one amino-H signal of Phenamacril is a result of a strong intramolecular hydrogen bond formed between this amino-H and either the nitrile or the ester H-bond acceptor moiety. Comparing the ^{1}H-NMR spectra of Phenamacril to those of **5 (ESI S16)**, the nitrile group does not seem to be capable of causing a high-frequency shift of the same magnitude as observed in Phenamacril (chemical shift of the amino protons of **5** in $CDCl_3$: 5.56 and 6.27 ppm), whereas the chemical shifts of the lower-frequency amino proton of **3** (chemical shift of the amino protons of **3** in $CDCl_3$**:** 5.10 and 8.98 ppm (ESI S12)), exhibit a higher similarity to the chemical shifts of the amino protons of Phenamacril, indicating that the ester moiety in Phenamacril is

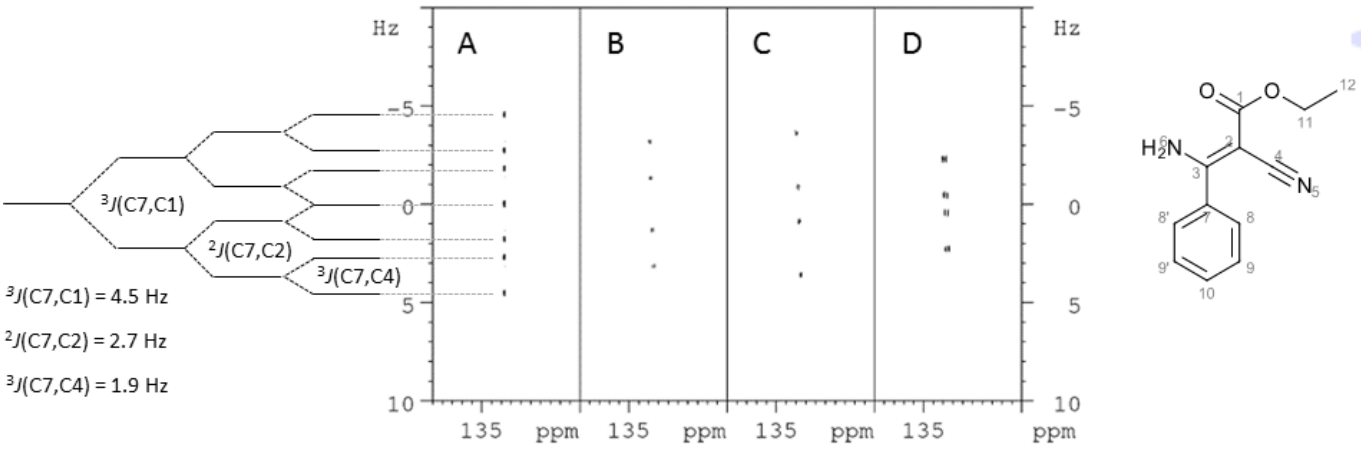

Figure 2. ^{13}C-2D-J-resolved NMR spectra of the C7 resonance of $^{13}C_{1,2,4}$-$^{15}N_5$-Phenamacril in $CDCl_3$ with ^{1}H broadband decoupling without (panel A) and with selective decoupling of C2 (73 ppm, panel B), C4 (118.4 ppm, panel C) and C1 (168.3 ppm, panel D) during the evolution time.

positioned *cis* to the amine, hence suggesting the *(Z)*-configuration. Our DFT calculations corroborate the (*Z*)-configuration as it leads to the lowest energies after geometry optimization (ESI S22). Moreover, the (*Z*)-configuration also yields the best agreement between experimental and calculated chemical shieldings. (ESI S23 – S29).

To determine the diastereomeric configuration of Phenamacril in solution once and for all, the vicinal ^{3}J(C,C) couplings between C7 and C1 and C4, respectively (numbering shown in Scheme 1) were exploited. The use of ^{3}J(C,H) coupling constants to distinguish *(E)*- and *(Z)*-geometries is not unusual.[50,51] However, the use of ^{13}C-^{13}C couplings is much less common, due to the low natural abundance of ^{13}C.[52] Vicinal coupling constants (^{3}J) depend on the dihedral angle between the coupling partners around the central bond in a manner described by the Karplus equation.[53] This is also the case for substituents of a C=C double bond, where ^{3}J(C,C) generally is smaller for *cis* couplings (θ=0°) than *trans* couplings (θ=180°) as e.g. shown for 3,3-dimethylacrylic and cinnamic acids,[52] compounds sharing some structural similarity with Phenamacril. For the *Z*-configuration of Phenamacril (**1a**), we therefore expect ^{3}J(C7,C1) > ^{3}J(C7,C4) and the opposite for the *E*-configuration (**1b**).

To obtain experimental values for these coupling constants, a selectively 1,2,4-^{13}C,5-^{15}N-labelled isotopomer of 2-cyano-3-amino-3-phenylacrylate was synthesized from ethyl cyano-^{13}C, ^{15}N-acetate-1,2-$^{13}C_2$, from which we determined the $^{3}J_{CC}$ of C7 to C4 and C1 (Figure 2) through a series of selectively ^{13}C decoupled ^{13}C-^{13}C J-resolved NMR experiments.

C7 displayed the expected coupling pattern of ddd (doublet of doublet of doublet). In order to assign the three observed couplings to the respective coupling partners (C1, C2 and C4; other C are at natural isotope abundance of 98.9% ^{12}C and can thus be ignored), we repeated the experiment with selective decoupling of each coupling partner during evolution. The experimentally determined coupling constant from C7 to the carbonyl C1 is 4.5 Hz, larger than the coupling constant to the nitrile C4 which is 1.9 Hz.

To confirm the coupling constant argument used in the structure elucidation DFT-calculations were performed (ESI S29). These computations of the vicinal coupling constants for both (*E*)- and (*Z*)-2-cyano-3-amino-3-phenylacrylate showed that in all cases $^{3}J(C7,C)_{cis}$ was significantly lower than $^{3}J(C7,C)_{trans}$. For the geometry-optimized structure of (*Z*)-Phenamacril, calculated coupling constants coincided within ±0.1 Hz with the experimental values. Thus, we conclude that the ester functionality is positioned opposite (*trans*) to the phenyl ring and the compound therefore assumes the (*Z*)-configuration (**1a**) in solution. Two different (*Z*)-configurations were considered, with the H-bond acceptor alternatively being the carbonyl or ester oxygen atom. The form with the carbonyl oxygen atom as H-bond acceptor (referred to as Z2) turns out to yield better matches for both the coupling constants and the calculated chemical shifts and is also the configuration with the lowest force field energy. To assess the importance of the intramolecular hydrogen bond for the structure of Phenamacril, *N6*-mono- and *N6,N6*-dimethylated derivatives of Phenamacril were synthesized. While the ^{1}H and ^{13}C-NMR spectra of the N6-mono-methylated derivative (**6)** do not differ much from the Phenamacril spectra, the *N6,N6*-dimethyl derivative (**2b**) shows a complete set of extra signals in both the ^{13}C (ESI S10 – S11) and ^{1}H-NMR spectra (Figure 1).

For *N,N*-dialkylated derivates, similar signal splitting was reported by Morel and co.-workers who ascribed it to the formation of both the *(E)*- and *(Z)*-isomer[41] and likewise observed by Jalander and Lönnqvist, who explained the phenomenon by restricted rotation.[42]

The ^{1}H-NMR spectrum of **2** (Figure 1 (iii)) clearly shows two sets of signals for the aromatic and ethyl group resonances and four sets of signals (with different line broadening at room temperature, but not at 240 K) for the N6-methyls, indicative of two intramolecular exchange processes going on; one of them being a rotation around the C3-N6 partial double bond. The other process could be a rotation around the C2-C3 or C1-C2 bond, both being represented as double bonds in some mesomeric forms and as single bonds in others. To find out, about which bond the rotation occurs, compounds **3** and **4** were synthesized (Scheme 1) and their ^{1}H and ^{13}C-NMR spectra compared. The methylations caused the two sets of ethyl-ester signals observed in **3** to collapse to a single set of signals in **4,** hence appearing "chemically equivalent", albeit broadened (ESI S12 – S15). For these ethyl-ester signals to coalesce, the rotation must take place around the C2-C3 bond. We therefore deduced that the second chemical exchange process, which causes the splitting of the ^{1}H- and ^{13}C-signals in the spectra (**2**) also takes place around the C2-C3 bond.

Exchange rates between the *(Z)* and *(E)* forms were investigated by Saturation Transfer NMR experiments. The signal intensities obtained in the saturation transfer experiment were converted to chemical exchange rates as described earlier.[54] Exchange rates determined at different temperature (ESI S20) yielded a molar activation enthalpy for the rotation around the C2-C3 bond of $\Delta H_a = 53.9 \pm 0.2$ kJ mol^{-1}.

In previous studies of bioactive 3-amino-2-cyanoacrylates the appearance of only one diastereomeric configuration during the synthesis of the compound was assumed to be owed to the reaction mechanism, where the nucleophilic amine moiety is being "guided" towards the substrate by hydrogen bond formation, thus resulting in the amine and ester moieties being positioned *cis* to each other.[33,35,39,40] However, our findings rather indicate that the predominance of one isomeric configuration is not a result of the reaction mechanism, but rather reflects thermodynamic stability. There is considerable rotational freedom around the C2-C3 partial double bond, and, if one configuration is energetically favored (e.g. because of hydrogen-bond formation), the equilibrium will be shifted towards that conformation, regardless of the initially formed diastereomer

Conclusion

In summary, using homonuclear ^{13}C-^{13}C J-resolved NMR and DFT-calculations of vicinal coupling constants, the correct stereochemical configuration of Phenamacril was finally determined as the *(Z)*-isomer and not the previously most often sketched *(E)*-isomer. Furthermore, this study showed the importance of the intramolecular hydrogen bonds in relation to the structures and dynamic properties of Phenamacril and its derivatives.

The findings are of huge interest to researchers in the field of fungicides in particular, as well as for research involving applications relaying on myosin inhibition, like the investigation of myosin inhibitors as anti-cancer drugs. The validity of results obtained from virtual screening/docking simulations of cyanoacrylates and myosin relies heavily on the knowledge of the stereochemically correct molecular structure of the small molecule ligands.

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There are no conflicts of interest to declare.

Keywords: 3-amino cyanoacrylates, cyanoacrylates, Phenamacril, myosine inhibitors.

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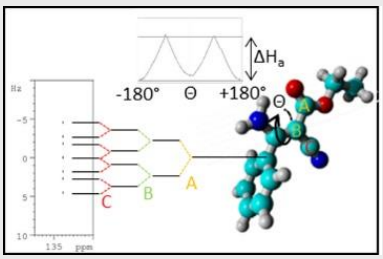
Entry for the Table of Contents

COMMUNICATION

More than a century after the discovery of 3-amino-2-cyano-acrylates, their correct stereochemistry is finally proven.



Stereochemistry of 3-Amino-2-cyanoacrylates

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