DOI: 10.1002/ejoc.200800710

Reaction of Carboxylic Acids with Isocyanides: A Mechanistic DFT Study

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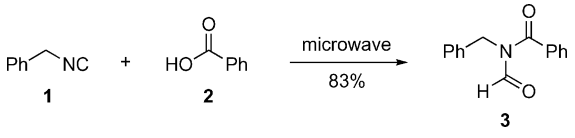
Keywords: Density functional calculations / Isocyanides / Reaction mechanisms / *E*/*Z* isomerism / Glycosylation

We present a computational investigation of the reaction between isocyanides and carboxylic acids. Our results indicate that this reaction begins with a stereoselective concerted α-addition of the acid to the isocyanide, leading exclusively to a *Z*-acyl imidate. Isomerization to the *E* isomer and successive rate-limiting 1,3 O→N acyl migration yields an *N*-formyl imide. The calculated barriers are in good agreement with the experimental reaction conditions. Our results might provide an explanation for the peculiar reactivity observed when this reaction is carried out in a self-assembled capsule.

Introduction

Isocyanides are intriguing compounds, whose unique reactivity has attracted the attention of synthetic chemists since their isolation in 1838.[1] In particular, it is the propensity of the terminal carbon atom to function both as a nucleophile and an electrophile (α-addition) that makes isocyanides extremely attractive starting materials for the generation of molecular diversity.[2] This distinctive behavior is exploited in popular transformations such as the Passerini[3] and Ugi[4] multicomponent reactions.

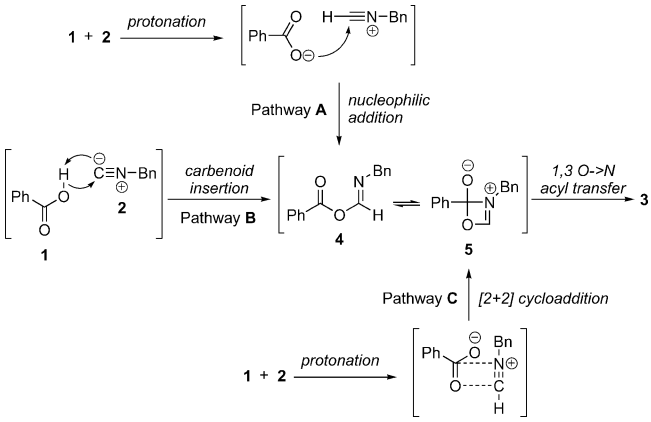
Recently, Li and Danishefsky reported that, when subjected to high temperatures, isocyanides react with carboxylic acids to selectively afford *N*-formyl imides in good to excellent yields (Scheme 1).[5] It is striking how this reaction could pass unnoticed in 170 years of isocyanide chemistry, especially when considering that carboxylic acids are the reaction partners of isocyanides *par excellence*.



Scheme 1. Reaction of isocyanides with carboxylic acids.

Besides its fundamental relevance in adding a new element to our knowledge of isocyanide reactivity, this reaction has a high synthetic potential. Li and Danishefsky showed that the resulting *N*-formyl imides can be readily elaborated into secondary amides, *N*-methyl, and *N*-hydroxymethyl tertiary amides; this latter class of compounds is particularly attractive as *N*-acyliminium ion precursors.[6] Furthermore, preliminary studies on model compounds highlighted the potential of this reaction for the highly stereo- and chemoselective synthesis of N-linked glycopeptides.[7]

Three mechanistic options were suggested for this reaction (Scheme 2):[5] protonation of the isocyanide and addition of the resulting carboxylate to the nitrilium (Pathway A); concerted carbenoid-like insertion of the isocyanide in the O–H bond of the carboxylic acid (Pathway B); [2+2] cycloaddition between the carboxylate and the nitrilium (Pathway C). All three pathways would lead to the formation of either acyl imidate **4** or heterocycle **5**, presumably in equilibrium, precursors for the 1,3 O→N acyl transfer leading to formyl imide **3**. Indirect evidence of the initial formation of an acyl imidate in the reaction mechanism was obtained by trapping this elusive intermediate with a nucleophilic amine and isolating the corresponding amide.[5]



Scheme 2. Previously proposed mechanisms for the formation of formyl imide **3**.

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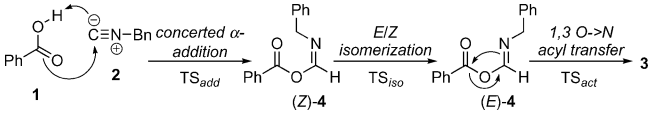
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

In this communication, we present a quantum chemical study of the reaction of benzyl isocyanide **1** with benzoic acid **2**. We find an alternative mechanism for the formation of formyl imide **3**, involving a stereoselective concerted α-addition followed by an *E*/*Z* isomerization and, finally, an 1,3 O→N acyl transfer (Scheme 3).



Scheme 3. Proposed mechanism (this work).

Results and Discussion

The B3LYP[8] density functional method as implemented in the Gaussian03 package[9] was used throughout the whole study. All structures were fully optimized by using the 6-31G(d,p) basis set. Final energies were obtained with the larger 6-311+G(2d,2p) basis set. All stationary points were confirmed by vibrational analysis and the final energies were corrected for zero-point vibrational effects. Solvation effects were included as single-point calculations by using the CPCM polarizable continuum model (ε = 4.9 for chloroform).[10]

The first step of Pathways A and C is the protonation of the isocyanide by the carboxylic acid. One can estimate the energy of this step by considering the relative acidities of these compounds. In water, the pK_a of benzoic acid is 4.8. On the basis of kinetic measurements of the acid-catalyzed hydrolysis of cyclohexyl isocyanide, the corresponding nitrilium was estimated to have a pK_a of 0.8.[11] The difference is thus ca. 4 units, which means that the energy of the carboxylate/nitrilium ion pair lies about 6 kcal/mol higher than the neutral reactants. In an apolar solvent such as chloroform this energy difference is expected to be even higher.

Every attempt to optimize the transition state for the proton transfer between the two reactants resulted, however, in a concerted α-addition of acid **2** to isocyanide **1**. This five-membered transition state (TS$_{add}$, Figure 1), leading to acyl imidate **4**, was calculated to have a barrier of 22.9 kcal/mol. A very interesting feature of this transition state is that, irrespective of the starting geometry employed, the addition of **1** and **2** always led to the formation of (*Z*)-**4**, indicating that this concerted α-addition is a stereoselective process. A similar observation has been made previously in theoretical studies of the reactivity of hydrogen isocyanide.[12] The phenomenon was rationalized in terms of stereoelectronic effects.

A second possibility for the formation of compound **4** involves insertion of the isocyanide carbon in the O–H bond of benzoic acid (Scheme 2, Pathway B). This transition state (TS$_{ins}$, see Supporting Information) was found to lie 6.3 kcal/mol higher (9.6 kcal/mol in gas phase) than *TS*$_{add}$, and also in this case (*Z*)-**4** was selectively formed.

In order for the acyl transfer to take place, the *E* isomer of acyl imidate **4** is required. We have located the transition

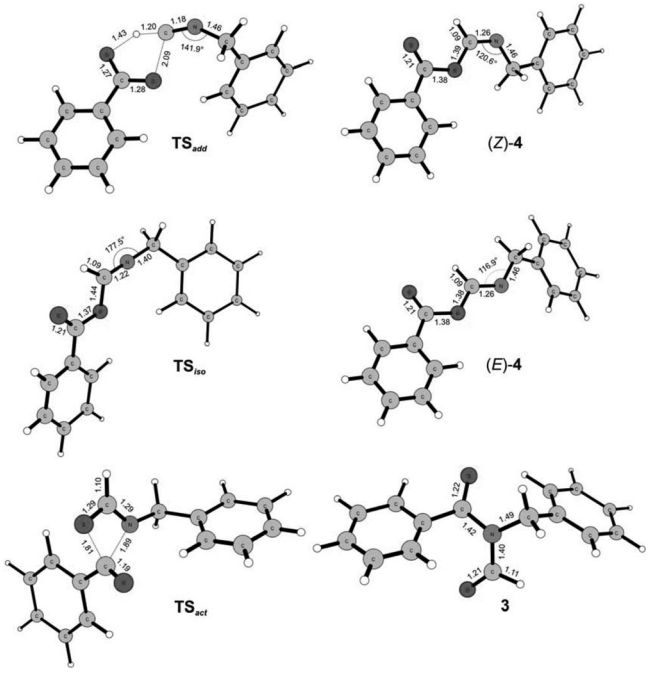


Figure 1. Optimized geometries of stationary points along the reaction path.

state for *E*/*Z* isomerization of the carbon–nitrogen double bond, which was found to occur by in-plane bending of the imine nitrogen – benzylic carbon bond (*TS*$_{iso}$, Figure 1). The calculated barrier for this process is 19.8 kcal/mol in chloroform, which demonstrates that the isomerization can take place readily under the reaction conditions. Next, the calculations indicate that conversion of imidate (*E*)-**4** into imide **3** takes place in one step through a four-membered transition state with concerted C–O bond breaking and C–N bond formation (TS$_{act}$, Figure 1). We found this acyl transfer to be the rate-limiting step in the process with a barrier of 26.0 kcal/mol in chloroform. Every attempt to optimize heterocycle **5** resulted either in imidate (*E*)-**4** or in formyl imide **3**.[13]

The overall reaction was calculated to be exothermic by 13.3 kcal/mol. The obtained potential energy profile for the full reaction mechanism of Scheme 3 is depicted in Figure 2.

Very recently, Rebek Jr. et al. reported that, in the presence of a self-assembled cylindrical capsule (**6.6**, see Supporting Information for the chemical structure), *n*-butyl isocyanide **8a** reacts with acid **7** at room temperature to cleanly afford *N*-formyl imide **9** (Scheme 4).[14] Remarkably, reaction of bulkier isocyanide **8b** had a different outcome, and formyl amide **11** was the only detectable product. NMR spectroscopic analysis of the reaction mixture showed signals compatible with acyl imidate **10**. Unfortunately, no information is available on the C=N bond geometry. However, the sharp isopropyl doublet signal in the ^{1}H NMR suggests that only one isomer of imidate **10** is present in the capsule.

Our mechanistic results might provide a plausible explanation for the difference in reactivity between isocyanides

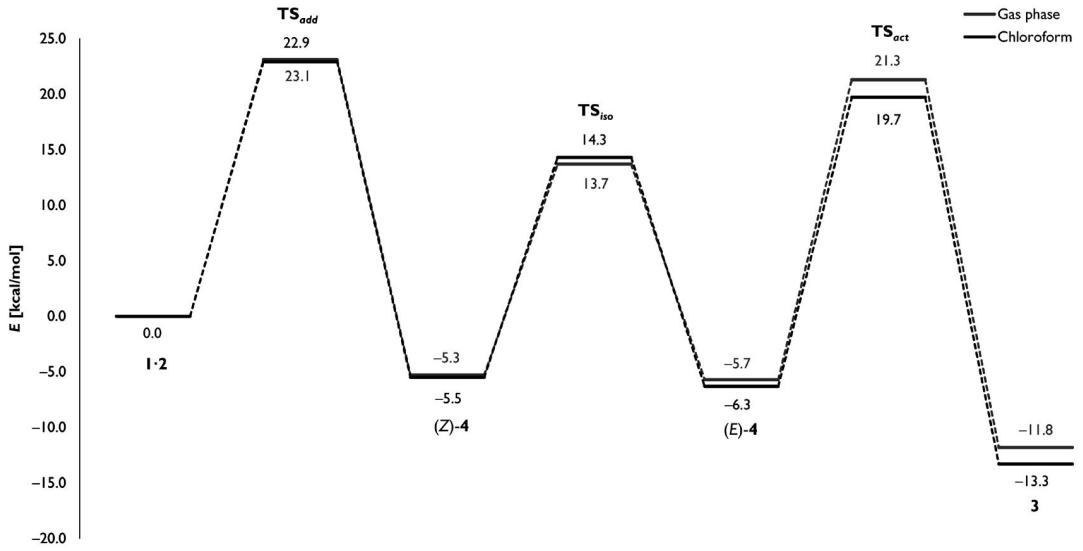
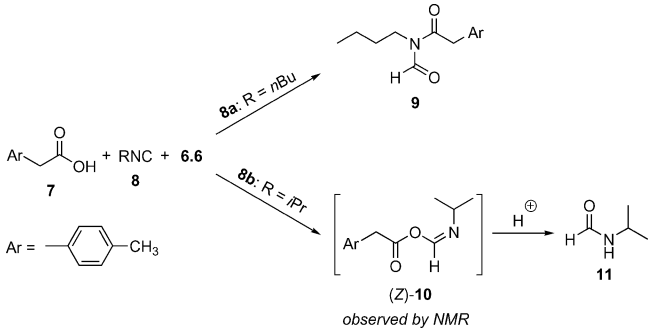


Figure 2. Calculated potential energy profile.



Scheme 4. Reaction of isocyanides with acid **7** in self-assembled capsule **6.6** (Ar = *p*-tolyl).[14]

8a and **8b**. Because the initial addition step leads exclusively to the *Z* isomer of the acyl imidate, it is possible that the following isomerization step can take place inside the capsule only in the case of isocyanide **8a**. The bulkiness of isocyanide **8b** could render the isomerization step inside the capsule too energetically demanding.

Conclusions

In conclusion, the DFT calculations presented here show that the reaction of isocyanide **1** with carboxylic acid **2** takes place through a concerted α-addition. This step was found to be stereoselective, leading to the exclusive formation of acyl imidate (*Z*)-**4**. The isomerization to compound (*E*)-**4** takes place by in-plane bending of the N–C bond. A concerted 1,3 O→N acyl transfer step, which is found to be rate-limiting, concludes the reaction. These results differ from the previous mechanistic proposals and could provide a rationale to interpret the outcome of the reaction of isocyanides and carboxylic acids in small spaces. We expect that these findings will aid the further improvement of this promising reaction.

Supporting Information (see footnote on the first page of this article): Geometry of TS$_{ins}$; structure of monomer **6**; cartesian coordinates and energies for all stationary points.

Acknowledgments

T. M. gratefully acknowledges the Wenner-Gren Foundation for a post-doctoral fellowship. F. H. gratefully acknowledges financial support from the Swedish Research Council (VR), the Wenner-Gren Foundations, the Carl Trygger Foundation, and the Magn Bergvall Foundation. We also acknowledge computer time provided through the Swedish National Infrastructure for Computing, SNIC 023/07-18.

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Received: July 17, 2008
Published Online: August 25, 2008
Minor changes have been made in this paper after its publication in Early View.

