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Revisiting the Passerini Reaction Mechanism: Existence of the Nitrilium, Organocatalysis of Its Formation, and Solvent Effect

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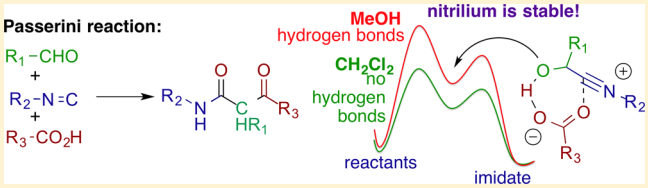
Supporting Information

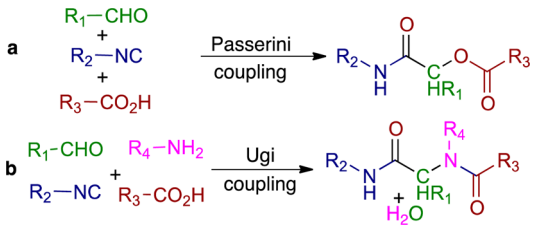
ABSTRACT: The Passerini reaction mechanism is revisited using high-level DFT calculations. Contrary to the common belief, the nitrilium intermediate is found to be stable in solution and its formation is rate-determining. The present results point out that this step is catalyzed by a second carboxylic acid molecule, as the subsequent Mumm rearrangement is. The solvent effect on the reaction rate was investigated. In a protic solvent like methanol, hydrogen bonds are responsible of the increasing barrier of the rate-determining step, compared to the commonly used solvent, the dichloromethane.



INTRODUCTION

In a context of rising environmental concerns, multicomponent reactions have been widely investigated during the past decades.[1] Among these reactions, isocyanide based multicomponent reactions (IMCRs) are particularly popular due to the carbenic reactivity of isocyanides.[2] The first IMCR was discovered by Passerini in 1921,[3] and involves an aldehyde, an isocyanide, and a carboxylic acid to form an α-acyloxy amide without any side product (see Scheme 1a).

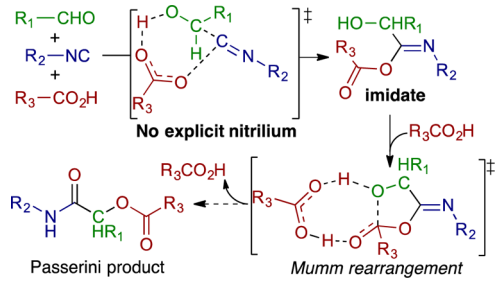
Scheme 1. Passerini and Ugi Couplings



Experimentally, the reaction was found kinetically favored in aprotic solvents (e.g., dichloromethane), while the closely related Ugi reaction (see Scheme 1b) has an opposite trend.[4,5] The Passerini coupling mechanism has been discussed in various studies.[6] Maeda et al. theoretically found with a *gas phase* calculation that the acyl-imidate formation step proceeds concertedly,[7] as widely represented in organic textbooks and publications (see Scheme 2). They also found that, contrary to the textbooks, the succeeding acyl transfer step, a Mumm rearrangement, requires a second acid molecule as a catalyst. Without it, the rearrangement cannot take place, which makes the Passerini reaction an organocatalytic reaction.[8]

In the present article, we wish to shed new light theoretically on the solvent effect on the Passerini reaction. Is it true that the nitrilium ion intermediate does not exist? Why is the reaction favored in aprotic solvents, i.e., why is it not favored in a protic and polar solvent like methanol, which is commonly used in the Ugi coupling?

Scheme 2. Commonly Admitted Passerini Reaction Mechanism



COMPUTATIONAL DETAILS

To investigate theoretically the origin of these unexpected behaviors, we chose the formaldehyde, methyl isocyanide, and formic acid as the reaction partners in dichloromethane and methanol as well as in gas phase. We used the recently developed AFIR search method[9] that enables automatic exploration of many different reaction pathways in conjunction with the density functional theory (DFT). Herein, the initial AFIR search was conducted using the M06-2X/6-31+G(d,p) level with PCM.[10,11] These approximate structures were then fully optimized without artificial force. The best pathways were then reoptimized using the mPW2PLYP-D/6-311++G(d,p) level.[12] When the second lowest pathway for a given step at the M06-2X/6-31+G(d,p) level was less than 1 kcal/mol higher than the lower one, both pathways were refined using the mPW2PLYP-D/6-311++G(d,p) level. This level of calculation was found to be in good agreement with the CCSD(T)//MP4(SDQ)/aug-cc-pVTZ level of calculation, which is considered as a reference as detailed in Supporting Information (see Tables S1−S4). Transition states optimizations were followed by IRC calculations to ensure connectivity of the reaction pathways. The

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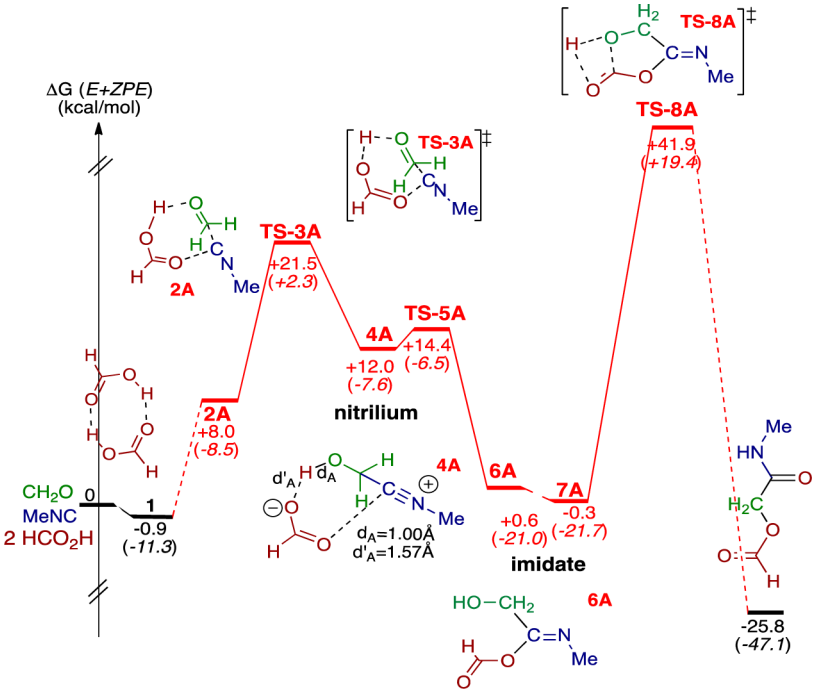
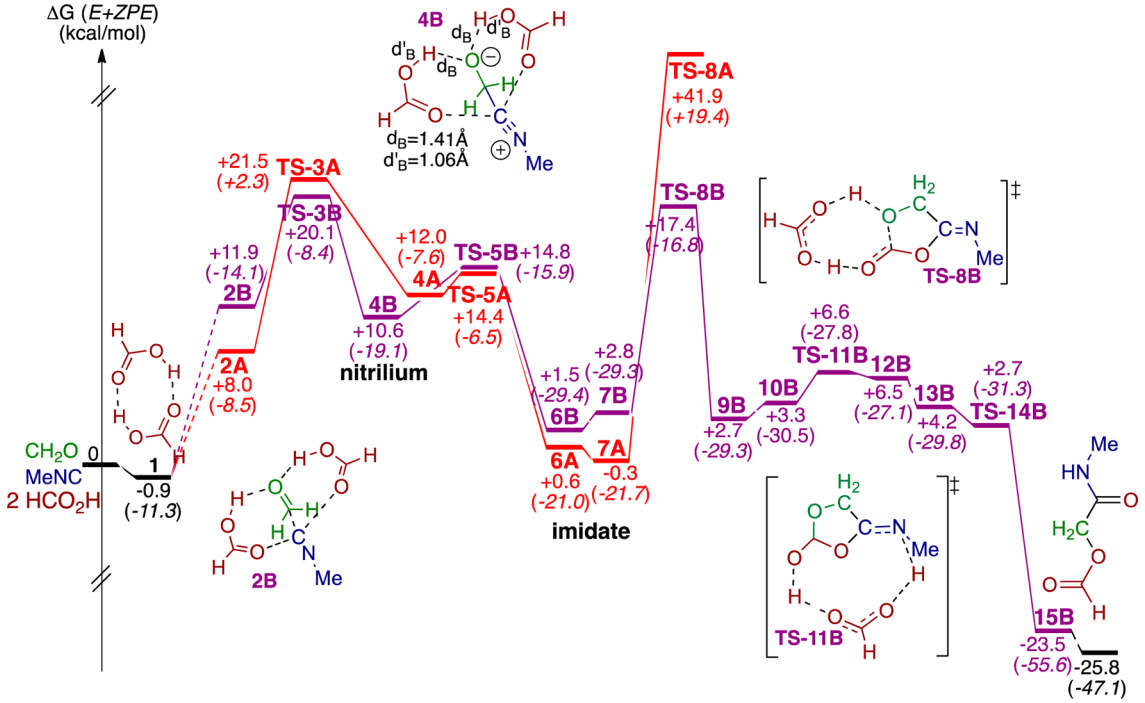
Scheme 3. Gibbs Free Energy Profile (E + ZPE) for the Three Components Reaction (in kcal/mol, Relative to Reactants at Infinite Distance) for the Passerini Reaction *in PCM Dichloromethane* (P = 1 atm, T = 298.15 K)



Scheme 4. Gibbs Free Energy Profile (E + ZPE) for the Three and Four Components Reaction (in kcal/mol, Relative to Reactants at Infinite Distance) for the Passerini Reaction *in PCM Dichloromethane* (P = 1 atm, T = 298.15 K)



energetic reference is taken as the carboxylic acid, isocyanide, and aldehyde separated at infinite distance. In all the calculations, the effect of bulk solvent was included using the Polarized Continuum Model (IEF-PCM). To investigate solvent effects not described by the PCM, some calculations have been performed including a few explicit solvent molecules. Electronic structure and Gibbs free energies were calculated with the Gaussian09 package.[13] Electronic energies with zero point correction (E + ZPE) and Gibbs free energies are given in the present figures, but only Gibbs free energies are discussed in the text (unless mentioned) to take into account entropic effects.

RESULTS AND DISCUSSION

In dichloromethane, two main approaches were used to study the reaction (see Schemes 3 and 4). In the first one, only three reactants are considered (path **A**, in red in Schemes 3 and 4; see also Figures S2−S3 and Tables S2−S4 in Supporting

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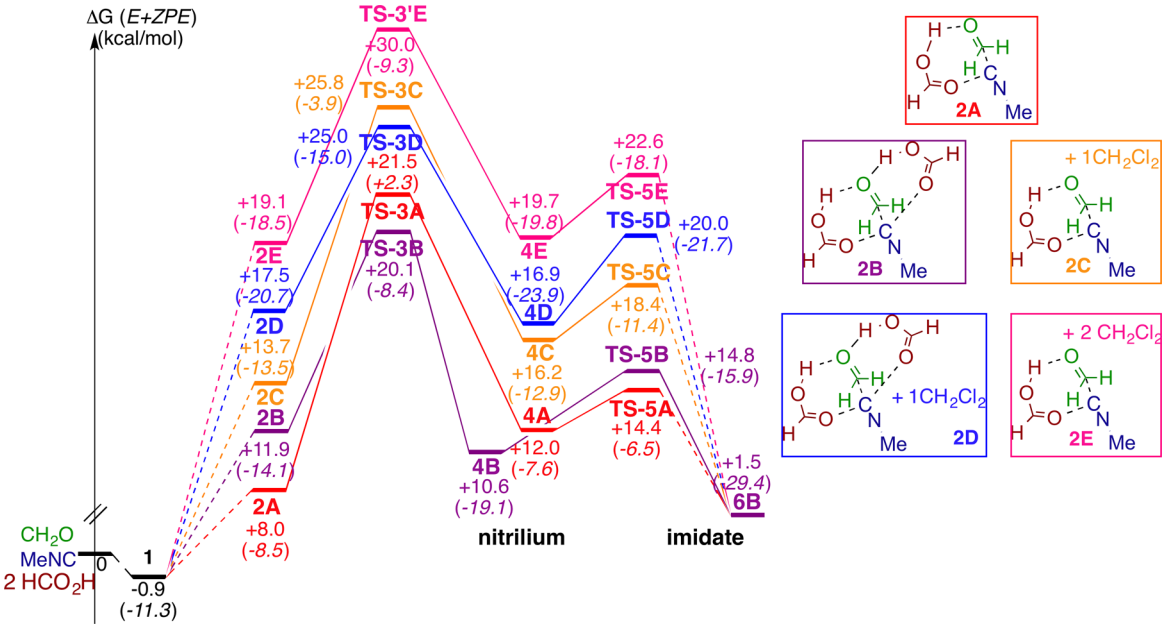
Scheme 5. Gibbs Free Energy Profile (*E* + ZPE) (in kcal/mol, Relative to Reactants at Infinite Distance) for the Passerini Reaction with *Explicit* and *PCM* Methanol Solvation (*P* = 1 atm, *T* = 298.15 K)



Information). In the second one, a second carboxylic acid is included as a catalyst (path **B**, in purple in Scheme 4). In path **A**, the first step starts with the prereactant complex **2A** of the three reactant molecules (higher than the isolated reactants in Gibbs free energy) and goes over the C−C bond formation transition state structure **TS-3A** to lead to a nitrilium−carboxylate ion-pair **4A**. The C−C bond formation between the isocyanide and aldehyde and the proton transfer from the carboxylic acid to the aldehyde takes place in one step. The free energy activation barrier is 21.0 kcal/mol (**1** → **2A** → [**TS-3A**]‡ → **4A**). With an additional formic acid (path **B**), a similar intermediate **4B** is formed. However, the proton transfer is not complete, and **4B** is a nitrilium zwitterion complex, stabilized by a double interaction with two formic acids. The transition state structure **TS-3B** is 1.4 kcal/mol lower than **TS-3A**, despite the entropy contribution of the second acid molecule. The next step is the C−O bond formation, which results in the acyl imidate formation (**4X** → [**TS-5X**]‡ → **6X**, **X** = **A**, **B**) with a relative low barrier (2.4, 4.2, kcal/mol for paths **A** and **B**, respectively). Then, the Mumm rearrangement occurs. This reaction from the acyl imidate **6A** has a 42.2 kcal/mol barrier at **TS-8A** and the reaction cannot take place. However, when a second carboxylic acid molecule assists the ring closing as a catalyst, the barrier is lowered (18.1 kcal/mol, **6B** → **7B** → [**TS-8B**]‡ → **9B**) and occurs rather easily. Then, a proton transfer from **9B** to the nitrogen is again catalyzed by the formic acid (barrier 3.9 kcal/mol via **TS-11B**). Finally, the ring is easily opened to form the final product (proton transfer and C−O bond breaking, **13B** → [**TS-14B**]‡ → **15B**). The overall process is highly exergonic with a 24.0 kcal/mol stabilization because of the formation of the very stable acyloxy amide. The steps from **6B** to the product in dichloromethane agree qualitatively with the previous gas phase finding of Maeda et al. (except that **15B** is reached directly from **TS-11B** in gas phase),[7] confirming that the Passerini reaction is an organo-catalyzed reaction.

To confirm that explicit solvation does not change the nature of the intermediates during the imidate formation, one dichloromethane solvent molecule is explicitly added to paths **A** and **B**, and paths **C** (in orange), and **D** (in blue) were found, respectively (Scheme 5). Path **E** (in pink) was obtained by adding two solvent molecules to path **A**. The barrier for the rate-determining step was found to be 26.7, 25.9, and 30.9 kcal/mol for paths **C**, **D**, and **E**, respectively. The next step is the C−O bond formation, leading to the acyl imidate intermediate (**4X** → [**TS-5X**]‡ → **6X**, **X** = **C**, **D**, **E**) that has a relative low barrier again (2.1, 3.1, and 2.9 kcal/mol for paths **C**, **D**, and **E**, respectively). The explicit solvation did not make any major change, and thus, paths **C**, **D**, and **E** were not studied further in dichloromethane.

It is noteworthy that, contrary to the common belief, our calculations indicate that the imidate formation is a stepwise process. The nitrilium complex (ion-pair or zwitterion) is predicted to be stable in solution, and its formation is the rate-determining step (RDS) of the process. The stability of this intermediate was confirmed by various density functionals (B3LYP, M06 family, ωB97X-D, B2PLYP-D3, mPW2PLYP-D), as well as ab initio calculations (CCSD(T)//MP4(SDQ)/aug-cc-pVTZ) as detailed in Supporting Information (Table S2−S5). Whatever the level of calculations, the minimum energy path (IRC) calculations from **TS-3X** lead to a nitrilium **4X** (**X** = **A** or **B**), although the present result suggests that a biactivation of the aldehyde through path **B** is more favorable over path **A**. If the electronic energy with zero point correction is considered, then pathway **B** is largely favored with a 10.7 kcal/mol energetic difference with pathway **A**. When considering Gibbs free energy, the energetic difference between the two pathways is only 1.4 kcal/mol in favor of **B** for both transition state structure and nitrilium species due to the entropic effects. Thus, pathway **A** cannot be completely excluded from these calculations. The most important finding here is that the nitrilium exists as an intermediate in solution. As the barrier to form the imidate from the nitrilium is not very large, it may be difficult to observe this intermediate experimentally. However, the nitrilium intermediate was isolated recently in the Ugi reaction despite a similar barrier

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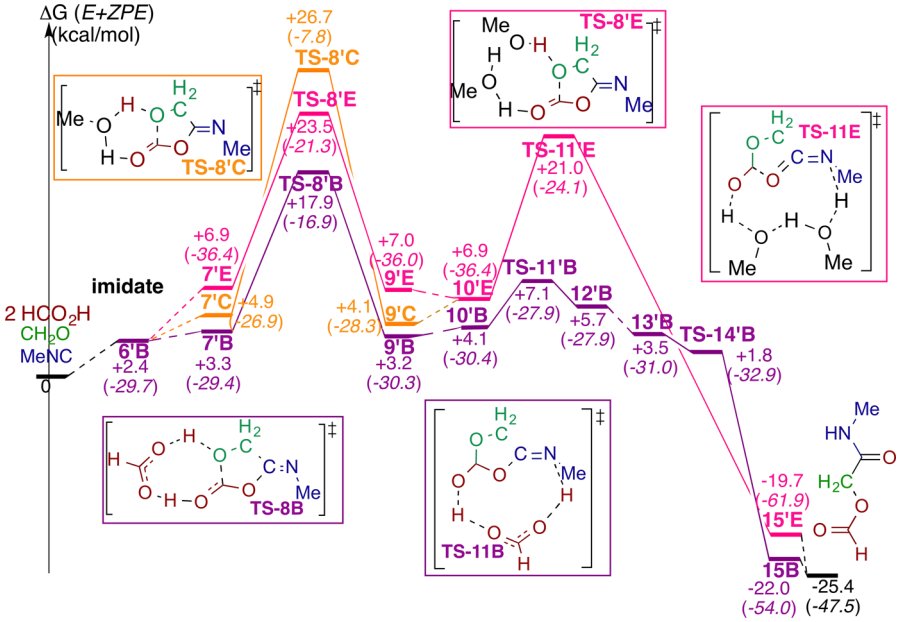
Scheme 6. Gibbs Free Energy Profile (in kcal/mol, Relative to Reactants at Infinite Distance) for the Mumm Rearrangement in the Passerini Reaction *in Methanol* (P = 1 atm, T = 298.15 K)



in methanol and the absence of its stability in toluene.[4,5] The previous calculations by Maeda et al.[7] performed *in gas phase* did not find any nitrilium intermediate. Our own calculations confirm this; the TSs located *in gas phase* from the prereaction complex **2A** or **2B** are concerted TS to produce the imidate **6A** or **6B** directly (see Figure S1 and Table S1 in Supporting Information). No stable nitrilium ion-pair or zwitterion was obtained in gas phase, even when we followed the minimum energy pathway (IRC) slowly.

In methanol, the solvent is hydrogen-bonding and PCM may not be enough to model correctly the solvent. Therefore, we also included explicit solvent molecule(s). We considered five pathways for the reaction: paths **A** and **B** with PCM as in dichloromethane and **C**, **D**, and **E**, which contain explicit solvation in addition to PCM. Path **A** with one free lone-pair of the oxygen can be excluded, as formaldehyde is likely to have two hydrogen bonds in methanol. The resulting pathways are close to those found in dichloromethane (see Supporting Information Figure S6). With two formic acids in path **B**, the transition state structure **TS-3′B** for the rate-determining C−C bond formation step is 1.2 kcal/mol higher than **TS-3B** in dichloromethane. This difference is consistent with the experimental trend. However, another functional (B2PLYP-D3) predicts a different trend as shown in Supporting Information. Thus, pathways involving explicit solvation need to be considered to understand correctly solvent effects. As in dichloromethane, paths **C**, **D**, and **E** were obtained by adding explicit methanol molecules from paths **A** and **B**. The first C−C formation step is still rate-determining, and the activation energies are 22.2, 26.7, 28.0, and 30.6 kcal/mol through **TS-3′X** (**X** = **B**, **C**, **D**, and **E**, respectively). The resulting nitrilium **4′X** (**X** = **C**, **D**, and **E**) are in the ion-pair form, as the carboxylate is stabilized by two hydrogen bonds with the nitrilium and the solvent molecules. It is noticed that the barrier for the C−O bond formation to give the acyl imidate is quite low again: 5.1, 1.5, 4.7, and 5.4 kcal/mol for **TS-5′X** (**X** = **B**, **C**, **D**, and **E**, respectively). As discussed above, the Mumm rearrangement cannot occur without catalyst. In methanol, the solvent itself can play this role (see Scheme 6). For one molecule of methanol, the activation energy for the ring closing is 21.8 kcal/mol (**7′C** → [**TS-8′C**]‡ → **9′C**). However, the next step, the ring opening, cannot occur easily due to the cyclic constraint. Thus, two molecules of methanol were considered for the rearrangement. The first step is easier and 16.6 kcal/mol are necessary to reach **TS-8′E**. From **9′E**, 15.5 kcal/mol are required to directly form the product. However, the path involving the second acid molecule via **TS-11′B** is still faster, for both ring closing and ring opening, and will be the dominant pathway of the Mumm rearrangement.

The comparison between methanol and dichloromethane solvent for the activation energies of the rate-determining C−C bond formation step is summarized in Table 1 for systems with the same number of partners. As already mentioned, the reaction is predicted to be favored in dichloromethane when four partners are considered (path **B**, 1.2 kcal/mol). However, as the B2PLYP-D3 functional does not predict this trend, a higher model for the system has to be considered. With five partners (paths **D** and **E**), only path **D** can be considered as the rate of path **E** is estimated to be 300 times lower than that in path **D** (see Supporting Information for the detailed calculation).[14] The energetic difference between the solvents is then increased. Path **D** is found 2.1 kcal/mol lower in energy in dichloromethane than in methanol. A 2.6 kcal/mol energetic

Table 1. Activation Free Energies (in kcal/mol) for the Rate-Determining Step (TS-3X and TS-3′X, X = B, C, D, E) in PCM Dichloromethane (DCM) and Methanol (MeOH)

system	pathways[a]	$\Delta G^{\ddagger}_{DCM}$	$\Delta G^{\ddagger}_{MeOH}$
4 partners	**B**: 1Al + 1RNC + 2Ac	21.0	22.2
	C: 1Al + 1RNC + 1Ac + 1S	26.7	26.7
5 partners	**D**: 1Al + 1RNC + 2Ac + 1S	25.9	28.0
	E: 1Al + 1RNC + 1Ac + 2S	30.9	30.6

[a]Al, RNC, Ac, and S stands for aldehyde, isocyanide, carboxylic acid, and solvent molecule, respectively.

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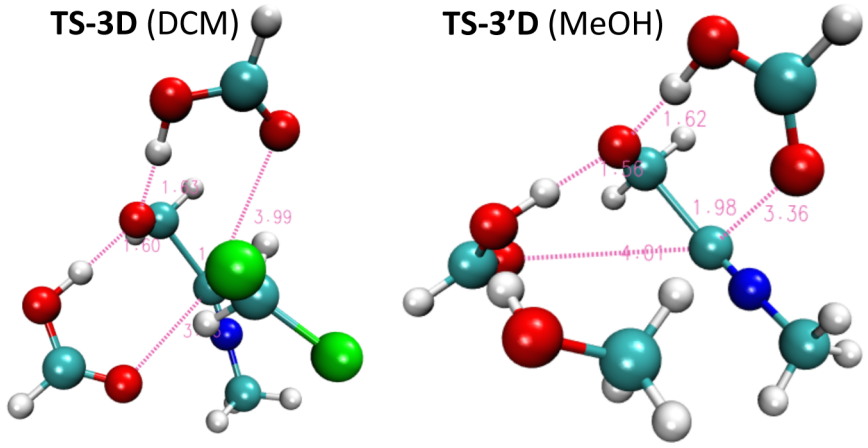


Figure 1. Transition state structures for the RDS in dichloromethane and methanol.

difference was found when using B2PLYP-D3, and confirms this result (see Table S6 in Supporting Information). From these two energetic differences, the rate of the reaction is predicted to be 35−80 times faster in dichloromethane than that in methanol (see Supporting Information the detailed calculation).

The origin of this difference was studied with an Energy Decomposition Analysis (EDA) on **TS-3D** (in dichloromethane) and **TS-3′D** (in methanol). In EDA, the reference was taken as two fragments: the fragment 1 consisting of the aldehyde and isocyanide and the fragment 2 consisting of the two carboxylic acid molecules and one explicit solvent molecule (see Supporting Information for the detailed calculations). While the deformation of the two fragments is more important in dichloromethane than that in methanol (+1.1 kcal/mol), a better interaction occurs in dichloromethane (−1.7 kcal/mol).

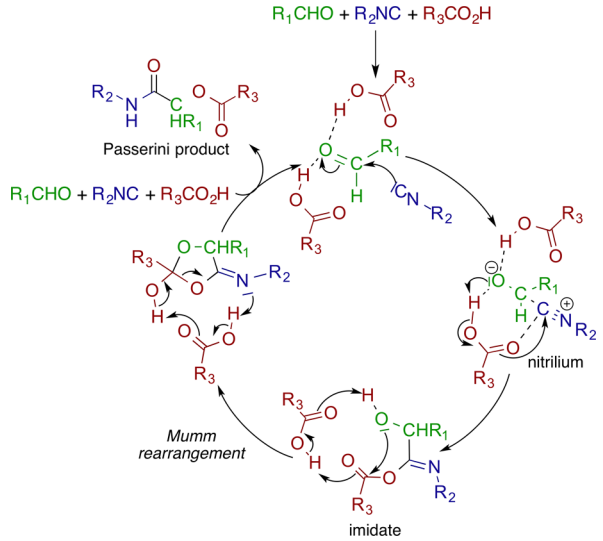
As shown in Figure 1, the interaction of the solvent with the reactant is different between the two solvents. In methanol, the hydrogen bond developed by the methanol molecule with the carboxylic acids breaks "the structural symmetry" found in dichloromethane, decreasing the interactions with the aldehyde. The aldehyde is then less electrophilic and the C−C bond formation is less favored in methanol, as observed experimentally. This result is confirmed by looking at the Mulliken charges: the carbons of the aldehyde and isocyanide are more electrophilic and nucleophilic, respectively, in dichloromethane than those in methanol (see Supporting Information Figure S6).

The ability of the aldehyde to create two hydrogen bonds explains why a different behavior is found between the Passerini and Ugi reactions. In the Ugi reaction, the RDS corresponds to the addition of the isocyanide on an activated *imine* by a carboxylic acid. By replacing the *aldehyde* in the Passerini reaction by an *imine*, only one lone-pair around the electrophile is then available in the Ugi reaction. With no hydrogen bond with a second molecule of acid or solvent molecule, the PCM approach is then enough to correctly model solvent effects for the Ugi reaction.[6a] Thus, with two similar mechanisms, the solvent plays a different role in these two couplings. While the higher is the solvent polarity, the better is the Ugi reaction; the aprotic property of the solvent is more crucial for the Passerini reaction.

CONCLUSION

To conclude, a revised mechanism for the Passerini reaction is proposed from the present results (see Scheme 7). Contrary to the common belief, the nitrilium species is stable in solution. The nitrilium existence was confirmed recently experimentally for the Ugi reaction, despite a very low barrier for the imidate formation.[5] This new result may encourage experimentalists to confirm the nitrilium existence in the Passerini reaction, as well as the revised mechanism.[15] Solvent effects observed experimentally were rationalized. The better efficiency of the Passerini reaction in aprotic solvents is not due to the nonexistence of the nitrilium, as always explained, but rather due to the absence of hydrogen bonds network with the solvent during the formation of the nitrilium, which would decrease the reactants reactivity.

Scheme 7. Revised Mechanism of the Passerini Reaction



ASSOCIATED CONTENT

Supporting Information

Methodology, rate estimations, EDA analysis, structures and Cartesian coordinates. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00594.

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Notes

The authors declare no competing financial interest.

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