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Challenging 50 Years of Established Views on Ugi Reaction: A Theoretical Approach

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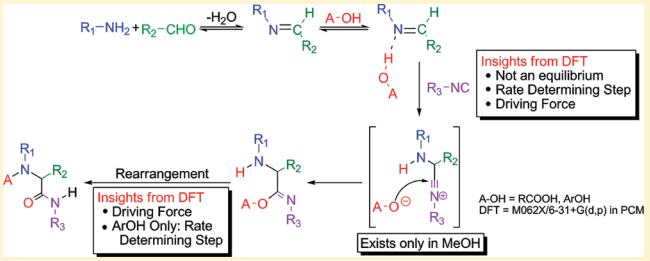
Supporting Information

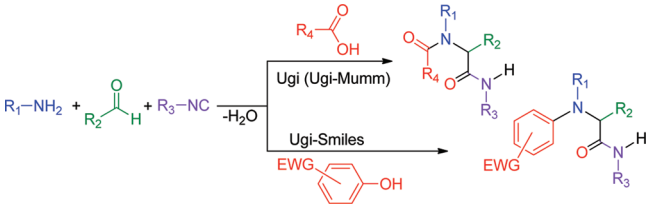
ABSTRACT: The Ugi reaction is one of the most famous multicomponent couplings, and its efficiency is still explained by the original mechanism suggested by Ugi in the 60s. This article aims to present a thorough theoretical study of this reaction. It describes how the imine is activated and how the new stereogenic center is formed. Our calculations strongly suggest alternatives to some commonly accepted features, such as the reversibility of the intermediate steps, and temper the nature of the driving force of the reaction.



INTRODUCTION

Multicomponent reactions (MCR) are processes in which three or more reactants are coupled at the same time to form one product including most of the atoms of the starting materials.[1] The development of combinatorial chemistry in the late 1980s revealed their tremendous potential and led to a renewal of the field.[2] In this context, isocyanide-based multicomponent reactions play a prominent role due to the efficiency of the Ugi coupling (see Scheme 1).[1,3] This reaction consists of the condensation of an amine, an aldehyde, an isocyanide, and a carboxylic acid to form peptidic derivatives. It has been used extensively to form various heterocyclic libraries, and its scope was further extended by using carboxylic acid surrogates such as HN_3 or phenols.[4,5]

Scheme 1. Ugi Reaction and Its Smiles Variant



Since its discovery in 1959, all synthetic developments around this reaction relied on mechanistic assumptions made by Ugi himself 50 years ago: a series of equilibria involving a nitrilium that is trapped by the oxygenated anion to give the corresponding imidate[6,7] as depicted in Scheme 2, path A. Such an ionic mechanism was postulated because of the greater efficiency of this MCR in polar protic solvents (such as methanol). More recently, an alternative mechanism was considered for the imidate formation involving the insertion of the isocyanide in a hemiaminal (see Scheme 2, path B).[8,9] In both cases, the last step is supposed to be an irreversible rearrangement displacing all the equilibriums by forming a CO double bond: a Mumm rearrangement[10] with carboxylic acids and a Smiles reaction[11] with phenols. Surprisingly, the Ugi–Smiles coupling was found to be efficient both in methanol and in aprotic media such as toluene. Another peculiarity of this four-component coupling is that the imidate intermediate could be isolated in some cases.[7]

We wish to present herein the first theoretical approach of Ugi-type reactions to answer several questions: What is the privileged mechanistic pathway, and do both Ugi couplings (Ugi and Ugi–Smiles) follow the same path? Why is the Ugi–Smiles imidate sometimes isolated? Most of the steps proposed by Ugi will be confirmed, although tempering the nature of the driving force of the reaction.

Recently, a theoretical study of the Passerini reaction[12] (a three component coupling between aldehydes, isocyanides, and carboxylic acids) was published by Maeda et al.[13] However, while the Passerini reaction performs only in apolar solvents, the Ugi one displays a different behavior, being much more efficient in protic solvents. The added amine responsible of these effects obviously leads to further complications for the theoretical approach, as multiple paths must be envisioned. In the present manuscript, we study both Ugi–Mumm and Ugi–Smiles reactions with a realistic model, using methyl groups for R_1, R_2,

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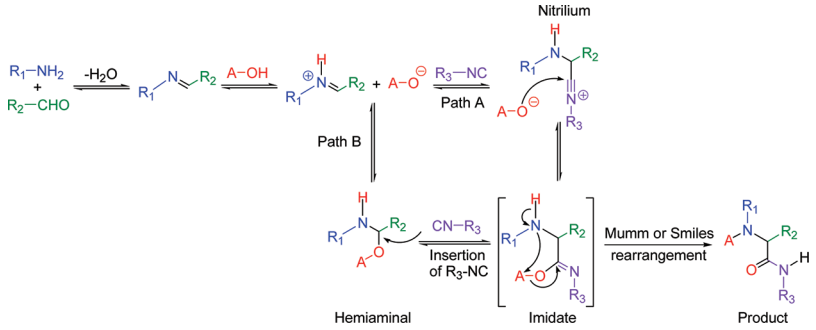
Scheme 2. Possible Mechanisms for Ugi-type Reaction[a]



[a]A–OH can be a carboxylic acid or an electron-poor phenol.

and R_3, in methanol and toluene. It can be shown that the two previous mechanistic hypotheses constitute the only plausible pathways (see the Supporting Information for details). The energy profiles are calculated at the M06-2X/6-31+G(d,p) level of theory including ZPE corrections, using an unbiased method (the string theory[14] as implemented in Opt'n Path[15]) to localize transition states (TS). As we are dealing with complex reactants, many relative orientations of the molecules were tried for each step. In the following energy profiles, only the most stable conformation of each structure is given, as all orientations are in equilibrium.

RESULTS AND DISCUSSION

Ugi–Smiles Reaction. Because of our ongoing interest in the Ugi–Smiles reaction,[5,7b] we were eager to address the mechanism of four-component couplings to better understand the differences and similarities experimentally observed between both Ugi-type reactions. Thus, we first investigated the mechanism of the coupling with phenols. The two pathways depicted in Scheme 2 were evaluated with the *ortho*-nitro phenol for A–OH, considering that the formation of an imine, a process already described,[16] constitutes fast preliminary steps. Moreover, both Ugi couplings can be experimentally regarded with an imine as starting input.[17]

In this study, the energy of the four reactants computed separately is taken as the reference. Optimization of the TS for the insertion of the isocyanide in the hemiaminal (path B) leads to the TS of the addition of the isocyanide in the iminium (path A). This is confirmed by performing intrinsic reaction coordinate (IRC) calculations on the former: it links the imidate to the nitrilium and not the hemiaminal. Thus, the insertion of the isocyanide involves first hemiaminal fragmentation into iminium and phenolate and subsequent isocyanide addition. Therefore, only one mechanistic path can be considered as valid for the Ugi–Smiles reaction, and all orientations of the reactants led to the same conclusions.

The most plausible energy profiles for the Ugi–Smiles reaction in methanol and in toluene are given in Scheme 3. Cartoons of the optimized intermediates and first TS structures in methanol are given in Figure 1. In both solvents, the reaction starts with the formation of an imine (**2**), which is then stabilized by hydrogen bonding with the phenol (**3**). A full energy profile involving (**2**) and (**3**) can be found in the Supporting Information. A prereactant complex (**4**) involving the isocyanide is then formed. The latter adds to the activated imine to create a new C–C bond, while the phenol proton is transferred to the nitrogen. In methanol, this step requires 15.8 kcal mol^{-1} of activation energy and leads to a stable nitrilium–phenolate ion pair (**5**) that will evolve easily to the imidate (**6**) with a 2.2 kcal mol^{-1} barrier. In toluene, the activation energy for the isocyanide addition is 18.4 kcal mol^{-1}. This addition leads directly to the imidate (**6**), as the nitrilium–phenolate ion pair is not stable in this apolar solvent. Let us note however that in both media, the proton transfer between the phenol and the imine occurs prior to the isocyanide addition; as illustrated in Figure 1, the NH bond is equal to 1.03 Å, while the OH bond is equal to 1.83 Å. Therefore, (**TS-1**) is best described as the addition of the isocyanide on the iminium hydrogen-bonded to the phenolate. (**6**) then undergoes the Smiles rearrangement to form a spiro structure (**7**),[11,18] with a 11.7 kcal mol^{-1} barrier in methanol and 13.7 kcal mol^{-1} in toluene. The spiro intermediate (**7**) then opens with a barrier of 7.3 kcal mol^{-1} in methanol and 7.5 kcal mol^{-1} in toluene. Because of the low barrier for the reverse transformation (**7** → **6**), this is equivalent to a concerted step with an activation energy of 16.6 kcal mol^{-1} in methanol and 20.5 kcal mol^{-1} in toluene. During the opening of the C–O bond, the proton of the ammonium is transferred, and the imidate (**8**) is formed. A final prototropy (not investigated here) leads to the product (**9**). Thus, two steps are found to be rate-determining for the Ugi–Smiles reaction with comparable activation energies (the isocyanide addition and the Smiles rearrangement), and being strongly exothermic, they also drive the reaction. Most noteworthy is the nonreversibility of the formation of the imidate as generally admitted. This result is of first importance, as it is during this step that the new stereogenic center is formed.

In the mechanism proposed by Ugi, the imine is activated by a proton transfer. Therefore, mechanisms involving iminium and phenolate were also investigated. First, we computed the relative energy of the proton transfer between the imine and the phenol to give an iminium and a phenolate. As the products are ionic compounds, they were solvated by explicit methanol molecules. The transfer is found to be unfavorable; when the reference is taken as the aldehyde, the amine solvated by one methanol molecule and the phenol solvated by three methanol molecules, the imine–phenol system (solvated by respectively one and three molecules) lies at −4.0 kcal mol^{-1}, whereas the iminium–phenolate system lies at −0.8 kcal mol^{-1}. We then considered a different path for the isocyanide addition on the iminium. If no phenolate is taken into account, the TS for the isocyanide addition on bare iminium lies at 16.4 kcal mol^{-1} in methanol and at 51.9 kcal mol^{-1} in toluene (to be compared with respectively 1.4 and 3.5 kcal mol^{-1}). Both activation

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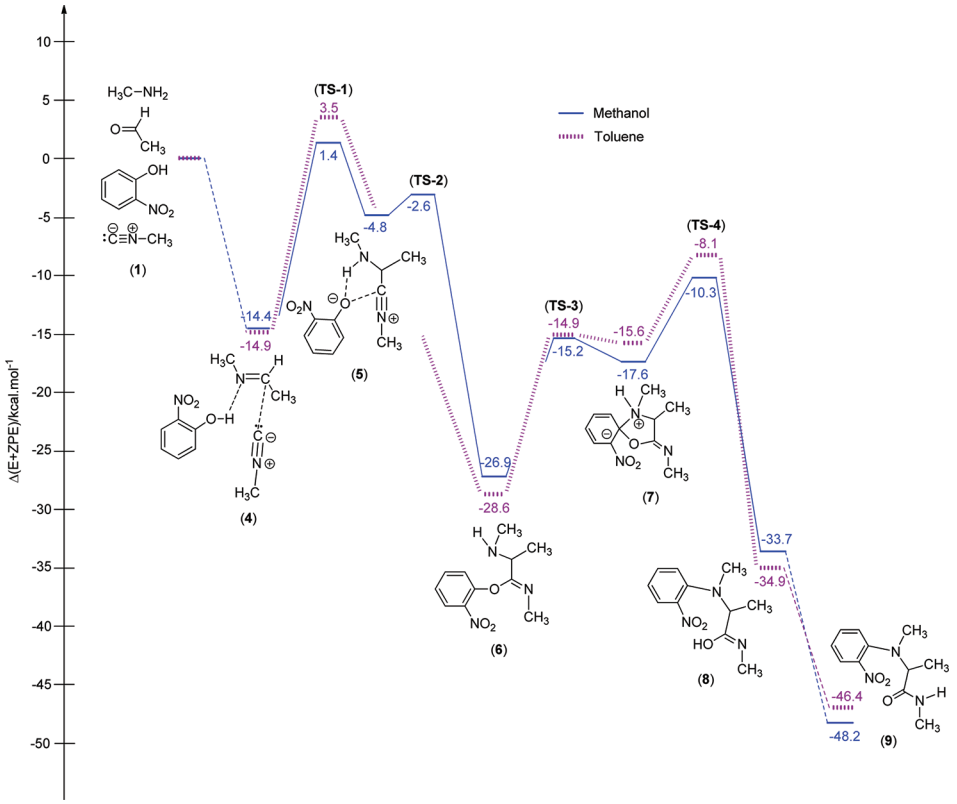
Scheme 3. Energy Profile of the Ugi–Smiles Reaction in Methanol and in Toluene[a]



[a]At the M06-2X/6-31+G(d,p) level of theory, including ZPE corrections. The energy reference is the sum of the four reactant energies computed separately. For the sake of clarity, the water molecule released in the imine formation is not displayed in the scheme.

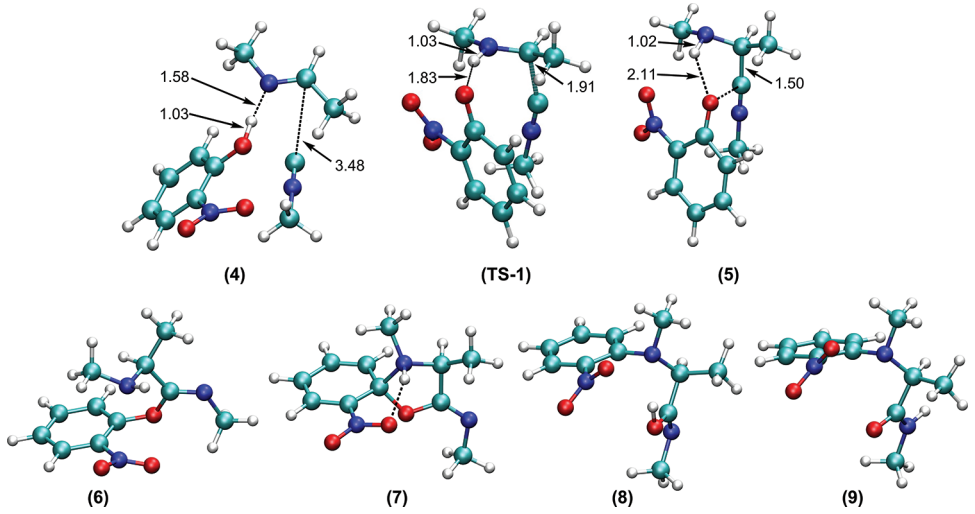


Figure 1. Optimized structures of the reaction intermediates and first transition state for the Ugi–Smiles reaction in methanol. Structures in toluene are very close. Interactive 3D structures are given for all reaction intermediates and transition states in the Supporting Information.

energies are much too high for these paths to be considered.[19] The imine is thus not activated by proton transfer but by hydrogen bonds; this is consistent with recent results reported by Fleischmann et al. while studying ion pairing by NMR spectroscopy.[20] Such a neutral activation process is logical in toluene but is also the main pathway in polar and protic solvents such as methanol. The main difference between the two solvents lies in the nature of the ion pair between the nitrilium and the phenolate in the energy profile, as it is an intermediate only in methanol. The mechanism for the imidate formation is thus nonionic in toluene.

Ugi–Mumm reaction. These results prompted us to investigate the classical Ugi reaction, in which acetic acid was chosen to model A–OH. As this reaction is very similar to the Ugi–Smiles one, similar structures will be denoted by adding a prime (′) to their name. Here again, for the formation of the imidate (**6′**), only one mechanistic path emerges from calculations, as path B was proved to also proceed through a first

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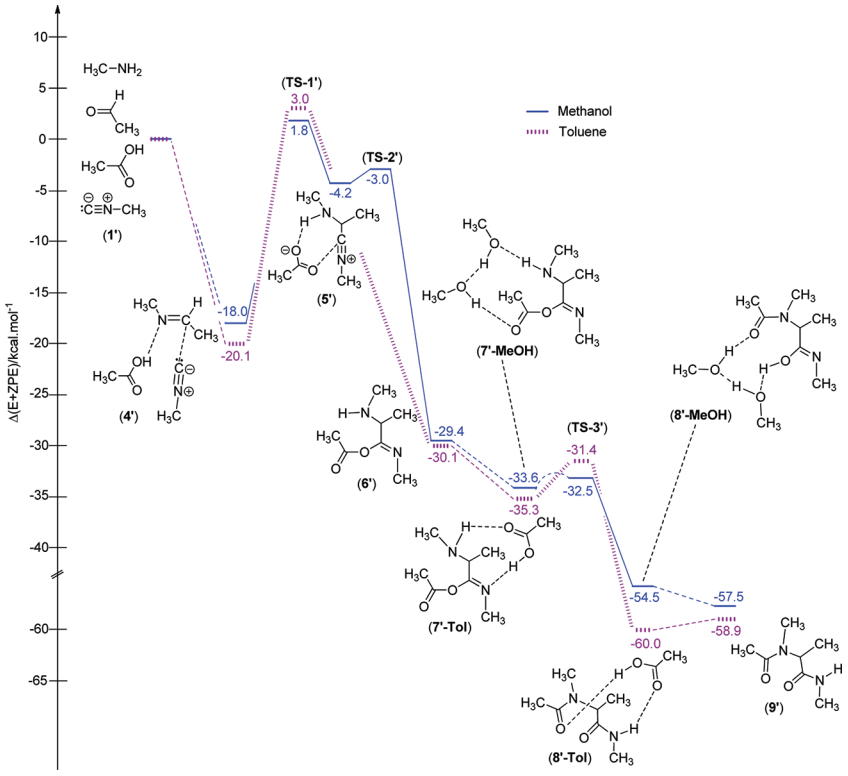
Scheme 4. Energy Profile of the Ugi Reaction in Methanol and in Toluene[a]



[a]At the M06-2X/6-31+G(d,p) level of theory, including ZPE corrections. The energy reference is the sum of the four reactant energies computed separately. For the sake of clarity, the water molecule released in the imine formation is not displayed in the scheme. When an extra carboxylic acid is involved, its energy reference is the one computed separately. When two methanol molecules are involved, their energy reference is a hydrogen-bonded methanol dimer computed separately.

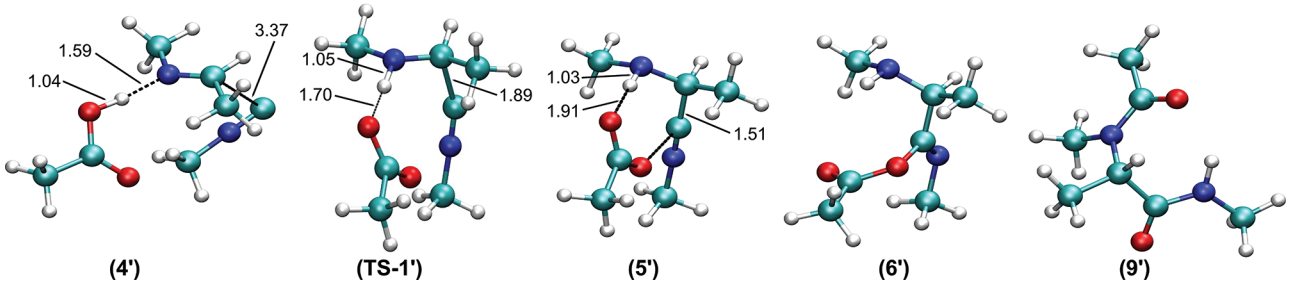


Figure 2. Optimized structures of the reaction intermediates and first transition state without microsolvation for the Ugi reaction in methanol. Structures in toluene are very close. Interactive 3D structures are given for all reaction intermediates and transition states in the Supporting Information.

fragmentation of the hemiaminal and then the isocyanide addition. In toluene, IRC calculations for some reactant orientations validate path B (isocyanide insertion in the hemiaminal); however, they are associated to barriers over 30 kcal mol^{-1}, which ensures the low probability of such paths.

The most plausible energy profiles for the Ugi reaction in methanol and in toluene are shown in Scheme 4, and some associated cartoons are depicted in Figure 2. Until (**6′**), the paths are similar to the Ugi–Smiles ones in both solvents. The activation energy for the isocyanide addition was calculated to be 19.8 kcal mol^{-1} in methanol and 23.1 kcal mol^{-1} in toluene, and no nitrilium–carboxylate ion pair (**5′**) is observed in toluene. Similar to the Ugi–Smiles case, the same discussion can be done for the imine/iminium difference, and the addition on the bare iminium is unlikely. Therefore, contrary to Ugi's proposal, the computed mechanism does not involve an intermediate iminium in both media and is found to be nonionic in toluene.

Maeda et al. demonstrated that for the Passerini reaction (which occurs only in apolar solvents), an extra carboxylic acid molecule is required, as a fourth partner, to allow the Mumm rearrangement to proceed.[13] A similar procedure was used in toluene, and we found that the Mumm rearrangement proceeds with a low barrier of 3.9 kcal mol^{-1} (see Scheme 4 and Figure 3). In protic polar solvent such as methanol, the proton transfer might also be mediated by the solvent itself; we thus have calculated the two energy profiles: both paths proceed with a low activation. With acetic acid, the solvated imidate lies at −31.9 kcal mol^{-1} and evolves with a barrier of 1.0 kcal mol^{-1}. Solvation by a methanol dimer is more favorable: the imidate lies at −33.6 kcal mol^{-1}, and the higest TS for the Mumm rearrangement is at −32.5 kcal mol^{-1}. The complete evolution

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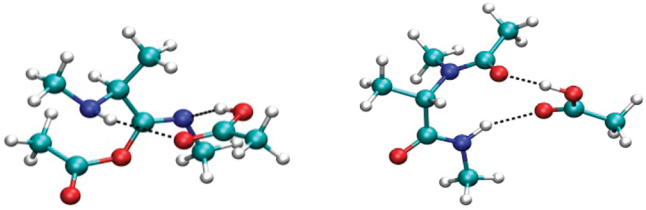


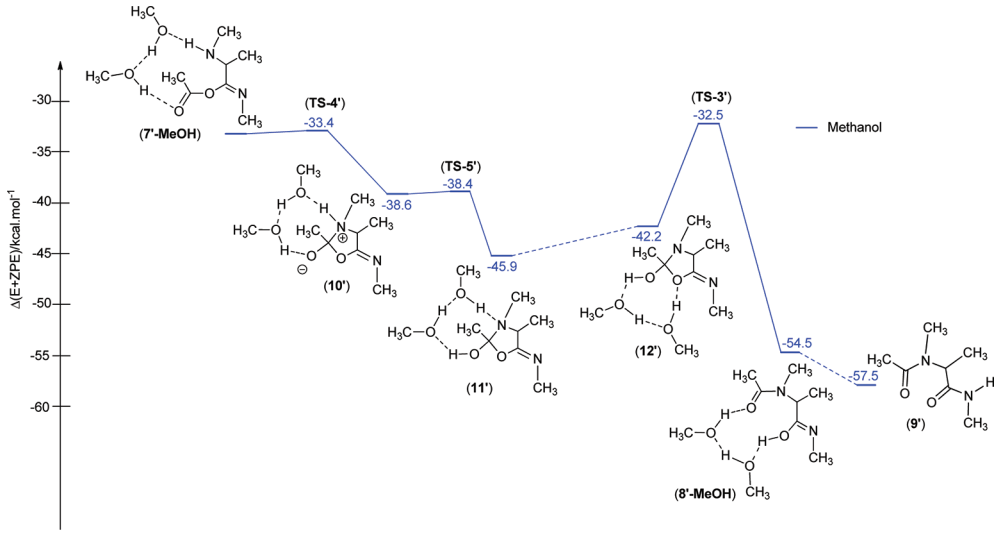
Figure 3. Optimized structures of the Mumm rearrangement with the system explicitly solvated by acetic acid in toluene. Structures in methanol are very close. Interactive 3D structures are given in the Supporting Information.

from (**7′-MeOH**) to (**8′-MeOH**) is described in the profile presented in Scheme 5, and associated cartoons are shown in Figure 4. Longer bridges (with more than two methanol molecules) are not as favorable because they are too flexible, whereas with one molecule, the bridge is too constrained. We also investigated other possible connections between nitrogen and oxygen atoms, but the one depicted in Scheme 5 is the most favorable one. In the Passerini reaction, the Mumm rearrangement performs between two oxygen atoms; at first order, this process is athermic (Maeda et al. found an exothermic reaction of 1.4 kcal mol^{-1} with a 38.3 kcal mol^{-1} barrier). In the Ugi reaction, the rearrangement occurs between an oxygen and a nitrogen atom and leads to the formation of an amide resulting in a highly exothermic process (by ca. 30 kcal mol^{-1}) and thus a lower activation energy.

These results demonstrate that the Mumm rearrangement can be done easily under acidic conditions and proceeds through very low barriers. In the Ugi reaction, the isocyanide addition turns out to be the only rate-determining step, and a 3.3 kcal mol^{-1} difference for the activation energy between methanol and toluene can rationalize the better efficiency of the reaction in protic solvents. As for the Ugi–Smiles reaction, the main difference between the two media is the nitrilium–carboxylate ion pair that is stable only in methanol. The formation of the imidate and the Mumm rearrangement are highly exothermic and finally drive the whole process. As such, our results suggest that the Ugi reaction should no more be considered as a sequence of equilibriums displaced by a final irreversible step as previously stated.

In the Ugi reactions, going from four reactants to two can have a dramatic effect on the entropy. The Gibbs free energy profiles are shown in the Supporting Information. The beginning of the free energy profile is above the reactants, but this is not problematic, as the reaction is more exothermic than the highest barrier.[21] It can be noted that from (**4**) to (**9**), the Gibbs free energy profile is almost the same as the (E + ZPE) one shifted by 27 kcal mol^{-1}, as after (**4**), only intramolecular reactions occur (see the Supporting Information).

Scheme 5. Energy Profile of the Mumm Rearrangement in Methanol with Explicit Solvation by Two Solvent Molecules[a]



[a]At the M06-2X/6-31+G(d,p) level of theory, including ZPE corrections. The energy reference is the sum of the four reactants and a hydrogen-bonded methanol dimer energies computed separately.

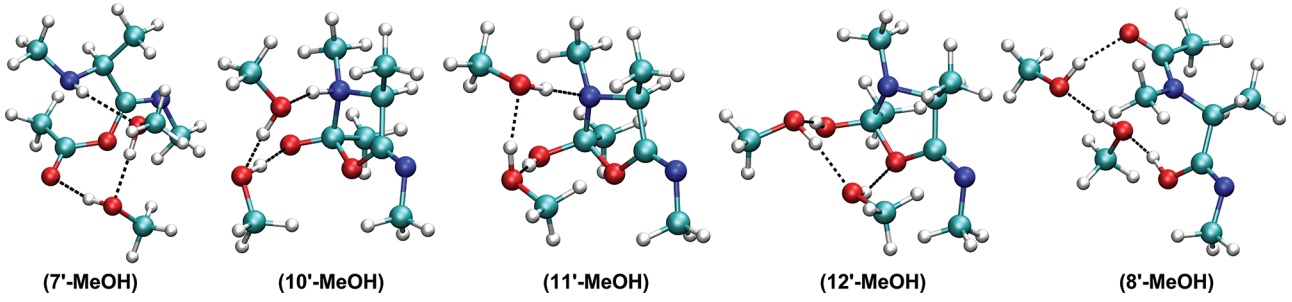


Figure 4. Optimized structures of the Mumm rearrangement with the system explicitly solvated by two methanol molecules. Interactive 3D structures are given in the Supporting Information.

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CONCLUSION

To conclude, this mechanistic study has shown that both Ugi and Ugi–Smiles reactions follow the same pathway. In particular, the activation process of the imine was clarified and consists of a hydrogen-bonded complex with the acidic substrate. The rate-determining steps were identified as well as the driving force of the process: in the most probable mechanism, the nitrilium formation does not proceed through an equilibrium. However, while the Mumm rearrangement is barely activated, the Smiles rearrangement is a rate determining step. These different behaviors explain the isolation of some imidates in the Ugi–Smiles coupling. In both processes, two steps are strongly exothermic so that the efficiency of Ugi-type reactions is not only linked to the final step. Moreover, the nonreversibility of the nitrilium formation also indicates that it should be possible to control the stereochemical outcome of the process. It will thus probably give new opportunities to settle the first enantioselective four-component coupling.

ASSOCIATED CONTENT

Supporting Information

Computational details. Systematic analysis of the possible reaction paths for the Ugi reaction. Cartoons of the optimized transition states structures in methanol. Full energy profiles and Gibbs free energy profiles. Comparison of energy profiles between E+ZPE and G energies while considering (**4**) as the reference. Interactive 3D structures. Cartesian coordinates for the structures discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org/.

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(19) If an explicit methanol molecule is added to form a hydrogen bond with the iminium, the TS energy increases to 18.3 kcal mol^{-1}, with the reference energy being the amine solvated by one methanol molecule, the aldehyde, the isocyanide, and the phenol molecules. This path is also unlikely.

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