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Formation of a vanillic Mannich base – theoretical study

Vladimir P. Petrović*, Dušica Simijonović, Zorica D. Petrović, Svetlana Marković

Faculty of Science, University of Kragujevac, Radoja Domanovića 12, 34000 Kragujevac, Serbia

One-pot *anti*-Mannich reaction of vanillin, aniline and cyclohexanone was successfully catalyzed by ionic liquid triethanolammonium chloroacetate, at room temperature. Yield of the obtained Mannich base was very good and excellent diastereoselectivity was achieved. Mechanism of the reaction was investigated using the density functional theory. The reaction started with a nucleophilic attack of aniline nitrogen at the carbonyl group of vanillin. The intermediate α-amino alcohol formed in this way was further subjected to protonation by the triethanolammonium ion yielding the imminium ion. Theoretically, the obtained imminium ion and the enol form of cyclohexanone can build the protonated Mannich base via the *anti* and *syn* pathways. The chloroacetic anion spontaneously abstracts the proton yielding the final product of the reaction *anti* 2-[1-(*N*-phenylamino)-1-(4-hydroxy-3-methoxyphenyl)]methylcyclohexanone (MB-H). The *syn* pathway requires lower activation energy but the *anti* pathway yields a thermodynamically more stable product, which implies that the examined Mannich reaction is thermodynamically controlled.
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Keywords: catalysis, ionic liquid, *anti*-diastereoselectivity, reaction mechanism, M052X functional

Introduction

Mannich-type reactions represent a very important strategy in the preparation of chiral compounds. Owing to these reactions, organic synthesists can build various magnificent nitrogen-containing molecules which are "architectural" blocks for the construction of many biologically active compounds and pharmaceutical products, such as nucleotides, peptides, alkaloids, steroid hormones, antibiotics, and vitamins (Arend et al., 1998; Touré & Hall, 2009).

Traditional catalysts for direct Mannich reactions of aldehydes, ketones and amines involve mainly Lewis or Brønsted acids (Loh et al., 2000; Akiyama et al., 2001; Manabe et al., 2001; Loh & Chen, 2002; Phukan et al., 2006; Yang et al., 2006). However, the use of these catalysts is followed by a number of serious disadvantages. Involvement of toxic organic solvents and difficult separation of products limit their use, especially in the synthesis of complex molecules. In the past decade, it has been noted that this reaction can be promoted by a wide range of catalysts such as

organocatalysts (Ibrahem et al., 2006; Janey et al., 2006; Kantam et al., 2006; Liu et al., 2007; Yang et al., 2007) and rare metal salts (Wang et al., 2005; Yi & Cai, 2006). In addition, ionic liquids (ILs) are considered as a promising alternative to conventional catalysts (Cole et al., 2002; Zhao et al., 2004; Sahoo et al., 2006; Dong et al., 2007). They have been proved to be highly active and selective, easily recyclable, and environmental friendly. Physico-chemical properties of ILs can be fine-adjusted by changing the structure of the cations and anions, depending on the purpose of the IL (Huddleston et al., 2001; Chiappe & Pieraccini, 2005; Shariati & Peters, 2005; Shariati et al., 2005; Zhao et al., 2005; Keskin et al., 2007). Besides the Mannich reaction (Cole et al., 2002; Zhao et al., 2004; Sahoo et al., 2006; Dong et al., 2007; Gong et al., 2007; Fang et al., 2009; Yue et al., 2009), ILs have found application in a wide range of other organic reactions (Abbott et al., 2002; Aggarwal et al., 2002; Kumar & Pawar, 2004; Xiao & Malhotra, 2005; Yin et al., 2006; Cota et al., 2007; Iglesias et al., 2010; Zhou et al., 2011). In transition metal catalyzed cross coupling reactions,

*Corresponding author, e-mail: vladachem@kg.ac.rs

such as those of Heck, Negishi and Suzuki, ILs have been extensively used as green reaction media (Singh et al., 2008). Synthesis of some ethanolamine based ILs and their application in the Heck reaction have been suggested by Petrović et al. 92010, 2012).

Mechanism of the Mannich reaction performed in the presence of different catalysts, such as proline (List et al., 2002; Parasuk & Parasuk, 2008; Chang et al., 2012), complexes of some metals and amines (Córdova, 2004), amino acids (Fu et al., 2008) and derivatives of urea and thiourea (Yalalov et al., 2008; Azuma et al., 2014), has been a subject of theoretical investigations. However, there are very limited data on the Mannich-type reactions catalyzed by ILs from biologically relevant ethanolamines (Abbott et al., 2002). Recently, details on the Mannich reaction catalyzed by some ethanolamine based ILs have been reported (Petrović et al., 2014). Excellent diastereoselectivity of the examined reactions was observed. Catalytic role of the applied ILs was elucidated by examining the mechanism of the model reaction of vanillin, 4-chloroaniline and cyclohexanone, implying that only the *syn* reaction pathway is to be considered. The present work is an extension of our investigations devoted to the explanation of the functional role of IL catalysts, and is focused on the *anti* reaction pathway. For this purpose, the reaction of aniline, vanillin, and cyclohexanone catalyzed by triethanolammonium chloroacetate ([HTEA][ClAc]) was examined using experimental and theoretical tools. Such selection was based on the fact that the reactions performed in the presence of this IL exhibited slightly higher yields in comparison to those presented in Petrović et al. (2014).

Theoretical

All calculations were carried out employing the Gaussian 09 program (Frisch et al., 2009) with the M052X functional (Zhao et al., 2006) and 6-311++G(d,p) basis set. Taking into account that the present study is an extension of our recent work (Petrović et al., 2014), the same level of theory was applied to achieve compatibility of the results. Geometrical parameters of all stationary points in ethanol ($\varepsilon = 24.3$) were optimized using the conductor-like solvation model (CPCM) (Barone & Cossi, 1998; Cossi et al., 2003). The choice of ethanol was based on the fact that the reaction was performed using ethanol as the solvent. All calculated structures were confirmed to be the local minima (all positive eigenvalues) for equilibrium structures or the first-order saddle points (one negative eigenvalue) for transition state structures by frequency calculations. The intrinsic reaction coordinates (IRCs), from the transition states down to the two lower energy structures, were traced using the IRC routine in Gaussian to verify if each saddle point is linked with two putative minima (Fig. S1). The natural bond orbital analysis (Gaussian NBO version) was performed for all structures.

Experimental

Synthesis of the Mannich product 2-[1-(*N*-phenylamino)-1-(4-hydroxy-3-methoxyphenyl)]methylcyclohexanone (MB-H) was performed using [HTEA][ClAc] as the catalyst (Simijonović et al., 2013). All components (aniline and vanillin (1 mmol), cyclohexanone (1.5 mmol), and ionic liquid as the catalyst (15 mol %)) were stirred in 1 mL of ethanol at room temperature for 24 h. The precipitated product was filtrated and washed with ethanol. The IL-catalyst was recovered by evaporating the solvent, and applied in a new reaction. No significant loss in the catalyst activity was observed (up to 5 % lower yield). Recrystallization from dichloromethane–propanol (2 : 1, vol.) yielded MB-H, which was analyzed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. All spectroscopic data as well as the ESI-MS spectrometric data were presented in our previous study (Petrović et al., 2014).

Results and discussion

In our previous study, catalytic role of monoethanolamine, diethanolamine and *N,N*-diethylethanolamine chloroacetates in the Mannich reaction was presented (Petrović et al., 2014). The present paper describes the catalytic role of triethanolammonium chloroacetate ([HTEA][ClAc]) in the reaction of vanillin, aniline and cyclohexanone. The reaction was performed at room temperature, and monitored by ^{1}H NMR spectroscopy. Analogically to the related works (Mukhopadhyay et al., 2009, Petrović et al., 2014), the characteristic area at 4,5–5 ppm was analyzed and only one doublet at 4.54 ppm (with the coupling constant value $J = 7.40$ Hz) was found, indicating the formation of the *anti* diastereoisomer of the Mannich product. It is worth pointing out that the *syn* isomer was not detected even in the ^{1}H NMR spectrum of the crude reaction mixture. The yield of the obtained *anti* 2-[1-(*N*-phenylamino)-1-(4-hydroxy-3-methoxyphenyl)]methylcyclohexanone (MB-H) was 94 %.

To explain the diastereoselectivity of the reaction, a mechanistic study of possible reaction pathways was performed. The first part of the reaction proceeds via the *R* and *S* routes, whereas there are *anti* and *syn* (*RS* and *SR*) routes in the second part of the reaction (Fig. 1). Intermediates and transition states in the *R* and *S* as well as in the *RS* and *SR* routes relate to each other as mutual mirror images and have thus identical energies. For the sake of clarity, only results for the *R* (Fig. 2) and *RS* (Figs. 3 and 4) pathways are presented. The crucial interatomic distances representing the evolution of bonds are listed in Table 1.
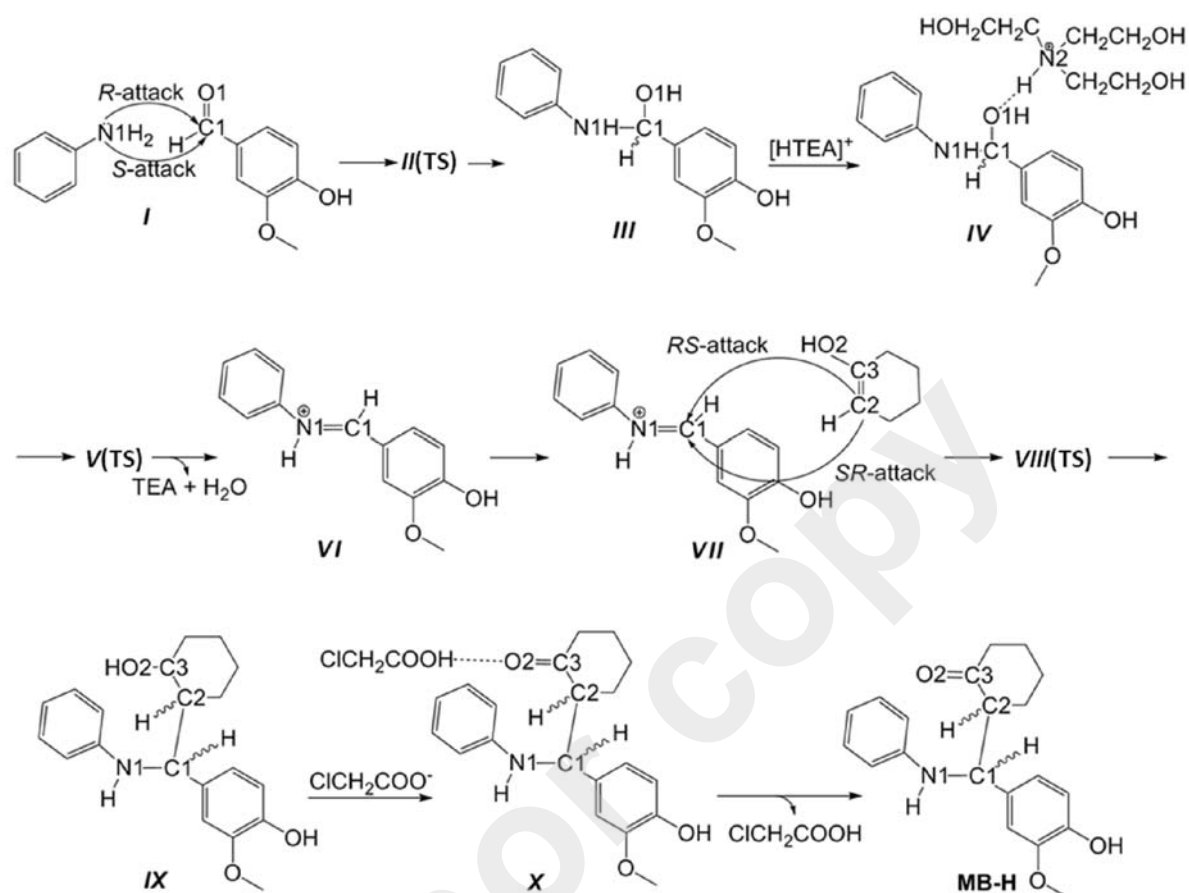
As it has already been shown in Petrović et al.

Fig. 1. Proposed mechanism of the Mannich reaction of vanillin catalyzed with [HTEA][ClAc].
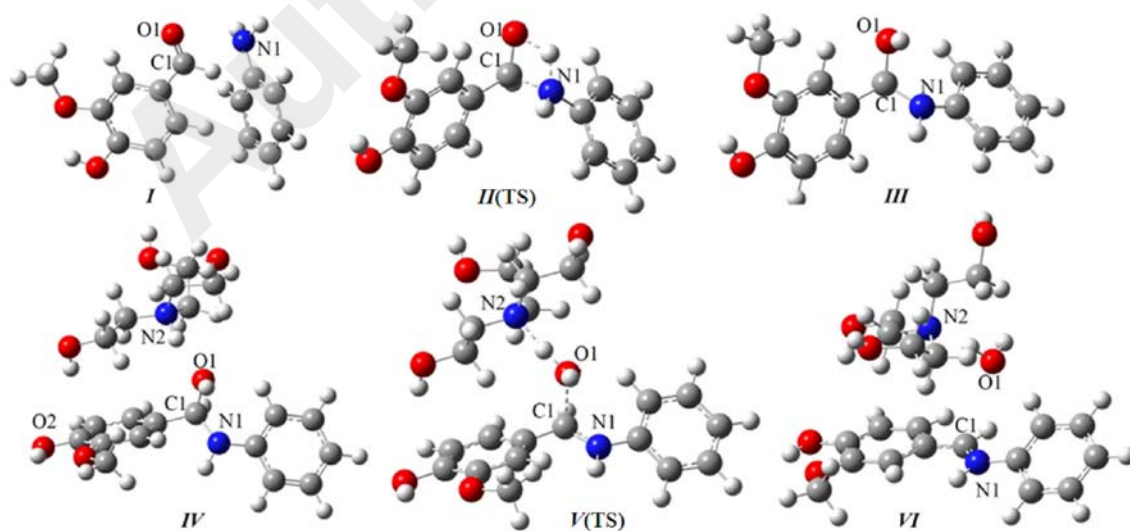

Fig. 2. Optimized geometries of substances involved in the R route of the examined reaction.

(2014), the reaction begins with a nucleophilic attack of the aniline nitrogen at the carbonyl group of vanillin forming an α-amino alcohol (*III* in Fig. 2). Based on the control experiments it could be stated that the formation of intermediate *III* is not a catalyzed reaction. Thus, when the equimolar amounts of aniline and vanillin were mixed together, the only product of the reaction was the Schiff base (modeled formation of the Schiff base is depicted in Fig. 5). In case when the catalyst is not present in the reaction mixture, *III* passes through a transition state that requires an activation barrier of 210.0 kJ mol⁻¹. This transi-
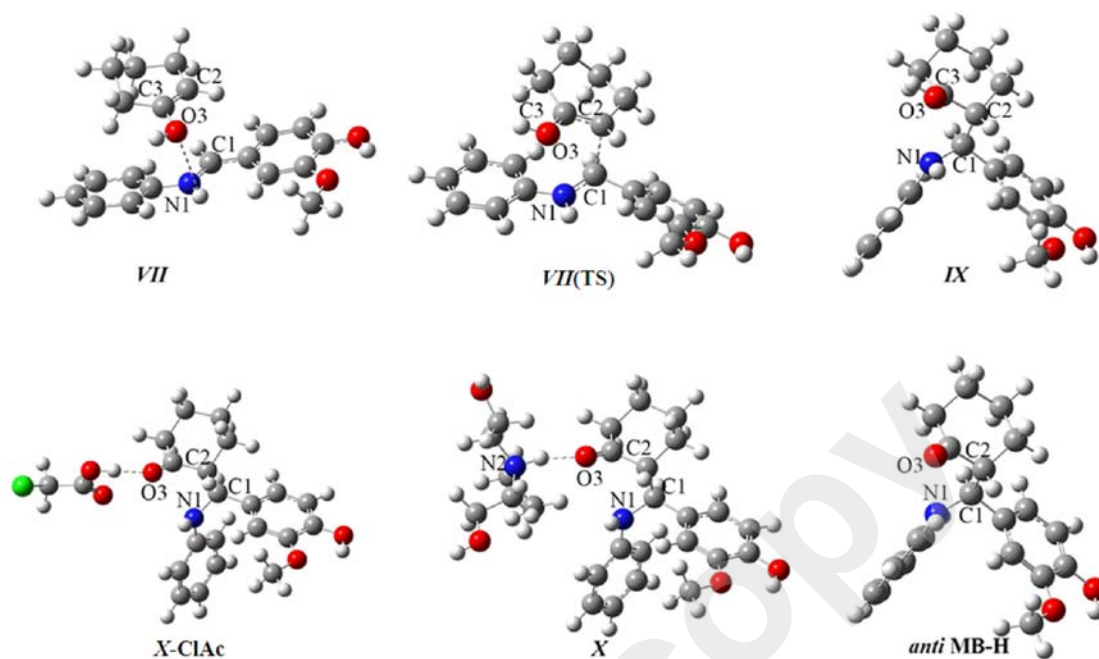
Fig. 3. Optimized geometries of substances involved in the *anti RS* route of the examined reaction.
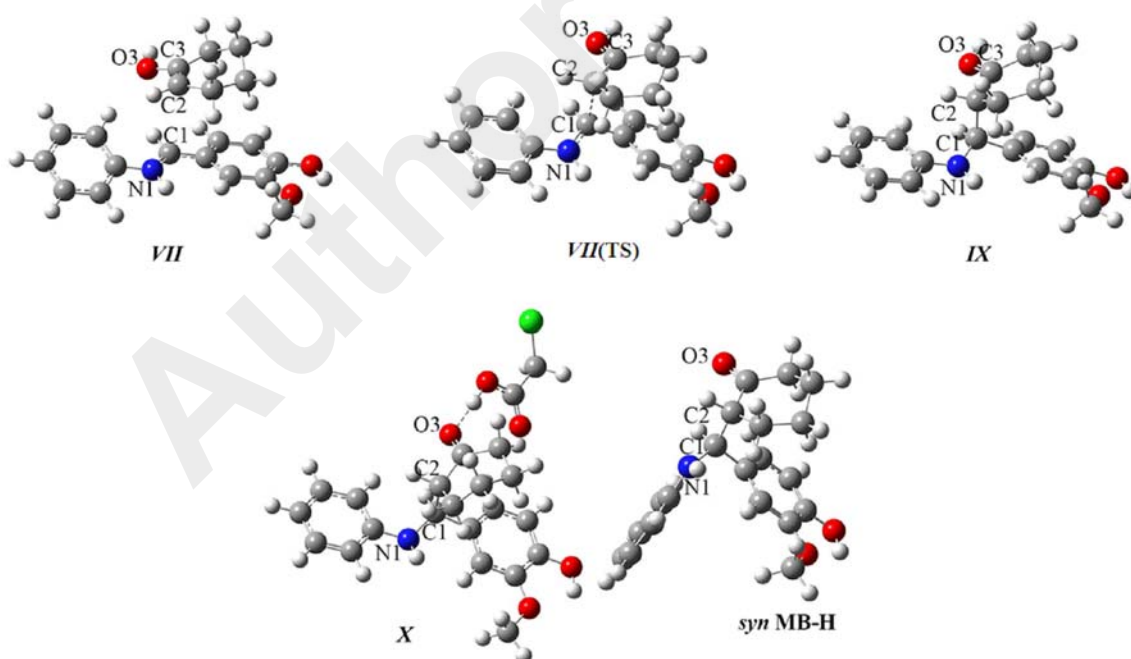

Fig. 4. Optimized geometries of substances involved in the *syn RS* route of the examined reaction.

tion state is characterized with simultaneous cleavage of the C—O and N—H bonds, and the formation of the O—H bond. These changes in chemical bonding lead to the liberation of a water molecule and the formation of the Schiff base. In addition, when the catalyst and cyclohexanone were added to the formed Schiff base, no further reactions occurred. On the other hand, when aniline, vanillin, cyclohexanone and a catalyst were mixed together, the Schiff base was not formed. These experimental findings indicate

a nucleophilic attack of N1 from aniline at C1 from the aldehyde group of vanillin as the first step of the reaction. This assumption is supported by the NBO charges of N1 (–0.824) and C1 (0.449). In addition, the HOMO map of aniline shows that HOMO is a delocalized orbital with significant contribution from N1, while the LUMO map of vanillin undoubtedly shows that the most electron deficient area in this molecule is C1 (Fig. 6). This interaction leads to the formation of *III* via the transition state *II*(TS) (Fig. 2), where

Table 1. Crucial interatomic distances (Å) in substances involved in the *R*, *anti RS* and *syn RS* pathways of the examined reaction

		N1—H	N—C1	O1—H	C1—O1	N2—H	O1—H
R	*I*	1.007	3.143	4.168	1.214	–	–
	II(TS)	1.209	1.567	1.368	1.367	–	–
	III	2.413	1.441	0.963	1.419	–	–
	IV	2.406	1.432	0.965	1.447	1.035	1.846
	V(TS)	2.832	1.328	0.965	1.893	1.449	1.104
	VI	4.783	1.296	0.960	3.084	1.816	0.990

		N1—C1	C1—C2	C2—C3	C3—O3	O3—H	O3—H(N1)
anti RS	*VII*	1.298	3.059	1.333	1.376	0.961	2.875
	VII(TS)	1.356	2.001	1.390	1.316	0.967	–
	IX	1.459	1.549	1.480	1.273	0.973	–
	X	1.455	1.546	1.509	1.223	1.647	–
	MB-H	1.456	1.517	1.545	1.215	–	–

		N1—C1	C1—C2	C2—C3	C3—O3	O3—H	
syn RS	*VII*	1.299	3.039	1.333	1.378	0.961	
	VII(TS)	1.361	1.974	1.388	1.315	0.967	
	IX	1.430	1.623	1.459	1.281	0.972	
	X	1.451	1.569	1.539	1.227	1.633	
	MB-H	1.452	1.553	1.541	1.215	–	
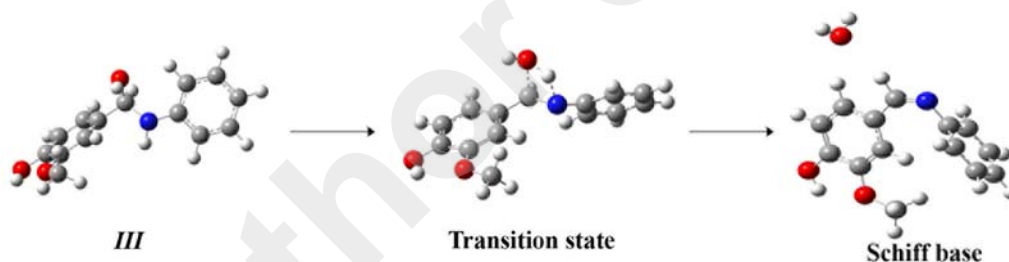
Fig. 5. Uncatalyzed dehydration of intermediate *III*.

the formation of a new N1—C1 bond, cleavage of the N1—H bond, and proton transfer to O1 of the vanillin carbonyl group occur simultaneously (Table 1).

III is further transformed in the presence of the IL catalyst. In our recent study, ethanolamine based ILs were proved to behave as separated ions in polar solvents (Simijonović et al., 2013). Bearing in mind that the reaction was performed in ethanol as the reaction medium, the presence of triethanolammonium cations and chloroacetic anions in the reaction mixture can be expected. Our calculation showed that [HTEA]$^+$ forms hydrogen bonds with *III*, yielding the intermediate structure *IV* (Figs. 1 and 2). There are two hydrogen bonds in *IV*: OH···O2 and N2H···O1, confirmed by the NBO analysis which revealed donation of electron density from the lone pair on O1 to the antibonding σ^* N2—H orbital, and from the lone pair on the phenolic oxygen to the antibonding σ^* O—H orbital from the [HTEA]$^+$ moiety. The next step of the reaction was a proton transfer from N2 to O1. This rearrangement was accompanied with the C1—O1 bond cleavage forming the imminium ion and a water molecule. These simultaneous processes occur through the transition state *V*(TS), and lead to the formation of intermediate *VI* (Fig. 2 and Table 1).

There are two possible reaction pathways: *anti* and *syn*. The structures involved in these two routes are presented in Figs. 3 and 4. It is assumed that in both cases the enol form of cyclohexanone attacks the C1 carbon of the imminium ion, forming the protonated Mannich base *IX*. The enol form of cyclohexanone is highly unstable (and therefore reactive) and, according to the Boltzmann formula, the keto/enol ratio amounts to 2.2×10^8. It should be pointed out that the enol form is spent in the reaction and thus the equilibrium is shifted towards the enol form. In accordance with this assumption, the NBO charge from the imminium ion on C1 is 0.287 and that from the enol form of cyclohexanone on C2 is –0.310. The LUMO and HOMO maps of the mentioned species show the electron most deficient and most sufficient areas in these molecules (C1 and C2 in Fig. 6). Therefore, formation of reactant complexes *anti/syn VII* can be assumed. In these reactant complexes, O3 from enol is involved in the hydrogen bond with H bonded to N1 of the imminium ion (Table 2). This hydrogen bond is
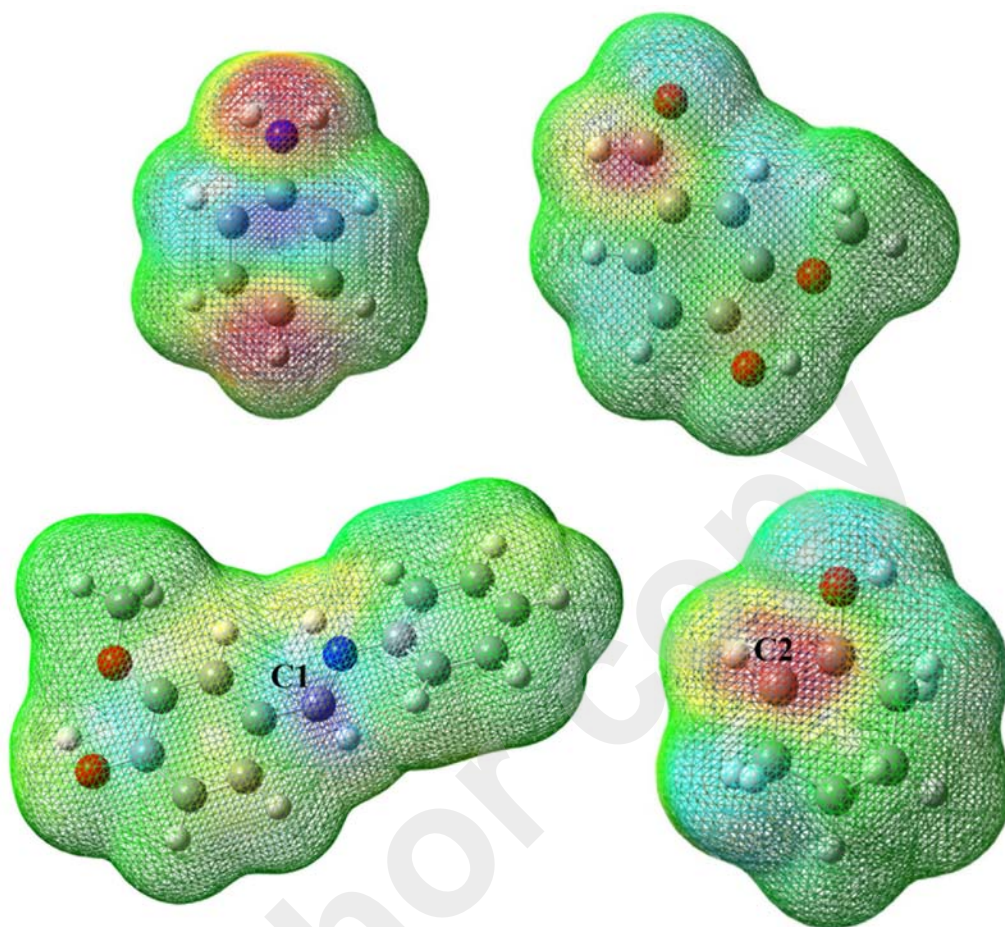
Fig. 6. HOMO map of aniline and LUMO map of vanillin (top), and LUMO map of the imminium ion and HOMO map of enol (bottom).

present only in the *anti* isomer. The transition state *VIII*(TS) was identified, where a new carbon–carbon bond (C1—C2) is formed while the π N1—C1 and C2—C3 bonds are cleaved. In this stage of the reaction, C1 and C2 become chiral (Fig. 1), which implies that C1 and C2 adopt the *S* and *R* configurations in the presented pathway (*RS*). In the intermediate *IX*, a new σ C1—C2 bond is completely formed while the π-bonds N1—C1 and C2—C3 are completely broken. O3 is still protonated. Numerous attempts to reveal a transition state structure for proton abstraction (O3—H) by the anionic part of the catalyst (chloroacetic anion) were unsuccessful. On the other hand, optimization of *IX* using the chloroacetic anion resulted in a spontaneous proton transfer from O3 to the oxygen of the chloroacetic anion, which led to the product complex *X*–ClAc. The structure of intermediate *X*–ClAc is characterized by the hydrogen bonds between the proton of the chloroacetic acid and the final product MB-H.

It is worth noticing that triethanolamine and chloroacetic acid, as precursors of [HTEA][ClAc], are liberated in the course of the reaction, which implies that the overall reaction results in the catalyst recovery. Our repeated experiments with recovered catalyst showed that the yields of so performed reactions were up to 5 % lower.

The reaction energetics is presented in Fig. 7. The overall reaction is exothermic due to the catalytic cycle. The rate determining step is the formation of the α-amino alcohol *III*. Activation energy of the uncatalyzed formation of the Schiff base (Fig. 5) is much higher than that required for the formation of the imminium ion *VI* in the presence of [HTEA][ClAc]. This finding confirms the role of the catalyst, and designates further transformation of intermediate *III* to MB-H. The *syn* pathway requires lower activation energy but the *anti* pathway yields a product which is thermodynamically more stable. These facts lead to the conclusion that the examined Mannich reaction is thermodynamically controlled.

Transition state *II*(TS) requires rather high activation energy. Considering that the cationic part of the catalyst (HTEA$^+$) is present in the reaction mixture, intermediate *I'* consisting of *I* and [HTEA]$^+$ (Fig. S2) was optimized. In spite of our expectation,
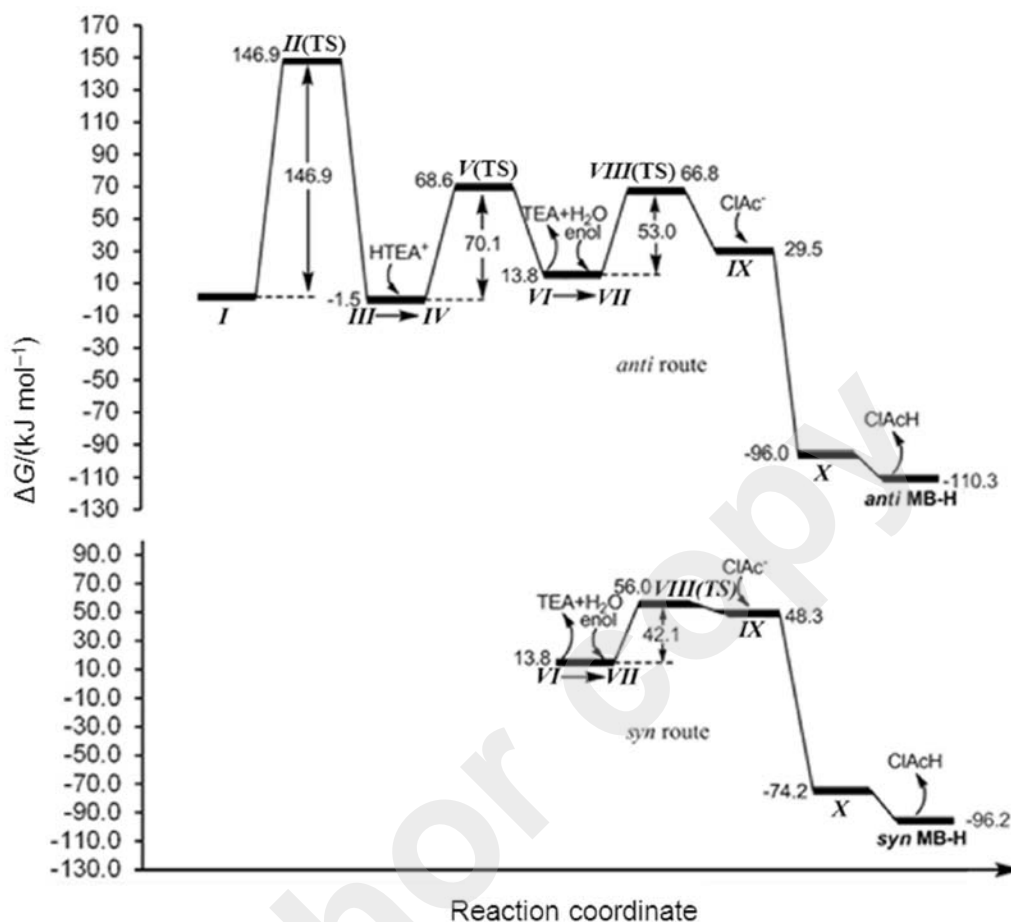
Fig. 7. Energetics of the Mannich reaction. Free energy values were calculated relative to that of *I*.

electrophilicity of C1 increased only slightly. In addition, our numerous attempts to locate the corresponding transition state were unsuccessful, probably because of the significant voluminosity of [HTEA]$^+$.

Conclusions

The diastereoselective Mannich reaction of vanillin, aniline and cyclohexanone catalyzed by triethanolammonium chloroacetate ([HTEA][ClAc]) at room temperature provided only the *anti* product. he reaction mechanism was examined using the M052X functional. It was shown that the formation of the intermediate imminium ion in the presence of [HTEA][ClAc] requires significantly lower activation energy than the alternative pathway, i.e. uncatalyzed formation of the Schiff base. The imminium ion reacts with the enol form of the cyclohexanone via the *anti* and *syn* routes. The *anti* route requires higher activation energy but yields a product of significantly higher thermodynamic stability in comparison to the hypothetic *syn* route. Since our experiments undoubtedly showed that only the *anti* isomer is formed, it can be concluded that the Mannich reaction catalyzed with [HTEA][ClAc] is thermodynamically controlled.

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