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A Recyclable Bifunctional Acid-Base Organocatalyst with Ionic Liquid Character. The Role of Site Separation and Spatial Configuration on different Condensation Reactions

Avelino Corma,* Mercedes Boronat, María José Climent, Sara Iborra, Raquel Montón, María J. Sabater

Instituto de Tecnología Química (UPV-CSIC), Universidad Politécnica de Valencia-Consejo Superior de Investigaciones Científicas, Avenida de los Naranjos s/n, 46022 Valencia, Spain.
Fax: 34 96 387 7809; e-mail: acorma@itq.upv.es

Abstract

A series of bifunctional organic catalysts containing acid and basic sites with ionic liquid characteristics have been prepared and their catalytic activity and reaction coordinate for aldol and Knoevenagel condensations have been compared. While the only factor controlling catalyst activity for Knoevenagel condensation was the distance between the acid and base sites, the spatial orientation of the organocatalyst is also key to achieve high activity and selectivity in the Claysen-Schmidt condensation. Mechanistic studies based on theoretical DFT calculations show that the acid-base bifunctional organocatalyst follows a mechanism inspired in natural aldolases for the synthesis of *trans*-chalcones, being able to produce a large variety of these compounds of industrial interest. The combination of the acid-base pairs within the proper

geometry and the ionic liquid nature, makes this catalyst active, selective and recyclable.

1. Introduction

Nowadays the design and synthesis of catalysts with well defined multiple active centres (acid, basic, redox, etc…) is an increasingly emerging field in chemistry. [1,2,3,4,5,6,7,8] The different active sites may be used to promote sequential transformations or to act synergistically to increase the rate and selectivity of a given chemical reaction. [9,10,11,12,13,14]

Multifunctional catalysis exhibits its best results when it comes to biological catalysts, i.e enzymes, as they exert their catalytic activity with extraordinary efficiency and selectivity due to their high recognition towards a determined substrate. [15,16,17,18,19,20] This particularity is due to the presence of functional groups structurally arranged in an optimal way in the active site, so that they interact with a given substrate more preferentially than with any other one. For achieving this, a proper distance and relative orientation of the functional groups in the active site is required, as it usually occurs in enantioselective reactions catalyzed by chiral transition metal complexes.[21] We will show here that a bifunctional acid-base catalyst with the adequate distance and orientation between the two sites, having at the same time characteristics of ionic liquids, can act as an efficient catalyst for aldol type condensations. While there are many homogeneous and heterogeneous catalyst which are able to catalyze condensation reactions, we want to show here that the activity of base organocatalysts could be improved by synthesizing bifunctional organocatalysts with acid and base sites. Furthermore it will be presented that while for some condensation reactions (Knoevenagel) the distance between the two sites is the determinant factor, there are other condensations in where the spatial orientation of the sites in the molecule is the

key parameter controlling activity and selectivity. This behaviour resembles that of some aldolase enzymes. Finally one of the problems associated with the use of organocatalysts, i.e. catalyst recovery, is solved here by preparing one organocatalyst with acid and base sites at a controlled distance and spatial orientation, hence showing ionic liquid features.

Claisen-Schmidt condensations between aldehydes and ketones to produce *trans*-chalcones will be used to present their potential advantage of the bifunctional catalyst with respect to the equivalent monofunctional base or acid organocatalysts (Scheme 1). Chalcones are important molecules with pharmaceutical applications as diuretic, choleretic, spasmolitic, antibiotic and antineoplasic, as well as for photoprotectors in solar creams plastics and food additives.[22,23,24,25,26,27,28] The acid-base bifunctional organocatalyst is able to synthesize a variety of *trans*-chalcones with good conversions and selectivities and, in any case, much more efficiently than the corresponding single site basic or acid catalysts. Moreover, the bifunctional catalyst with ionic liquid characteristics can be easily recovered and reused.

INSERT Scheme 1

2. Experimental Section

2. 1. General procedure for the Claisen-Schmidt reactions

In a typical experiment 1 mmol of the catalyst (previously activated for 2h at 80ºC under vacuum) was added to a solvent free solution of acetophenone (28 mmol) while stirring under inert atmosphere. The aldehyde (32 mmol) was added at the reaction temperature being the products periodically monitored by GC.

2.2. Recovery and recycling of bifunctional catalyst 1

After the first use was completed, the reaction mixture was treated with diethyl ether (3 x 50 ml) and two different phases separated. The ethers extracts were collected and the remaining crude, which contained catalyst **1**, was solved in dichloromethane and dried with ammonium sulphate anhydrous. The solvent was eliminated under vacuum and the residue was dried at 50ºC under vacuum for 2h.

2.3. Theoretical Basis

Calculations were carried out by means of the Gaussian03 program package[29] using the density functional B3PW91 method[30,31] and the standard 6-31G(d,p) basis set.[32,33] The geometries of all species considered were fully optimized and the nature of every stationary point was characterized by means of frequency calculations and analysis of the vibrational modes. Additional geometry optimizations starting from the transition states were performed to know which are the reactants and products linked by a specific transition state. Zero-point vibrational energy (ZPE) corrections to the total energies were obtained from frequency calculations.

3. Results and Discussion

Class II aldolases are metalloenzymes that catalyze stereospecific aldol reactions in micro-organisms (fungi, bacteria, blue-green algae) in a reversible manner. They introduce a bifunctional catalytic system formed by a basic group for abstracting a proton from a ketone, and a transition metal ion (usually Zn^{2+}) as Lewis acid cofactor to facilitate deprotonation and to generate a Zn^{2+}-enolate (step **I** in Scheme 2a).

INSERT Scheme 2

This nucleophilic enediolate attacks the carbonyl group of an oncoming aldehyde that is activated by an acid carboxylic group (step **II** in Scheme 2a), hence assisting the formation of the new carbon–carbon bond and thereby the formation of a new aldol product (see steps **III** and **IV** in Scheme 2a). By means of this bifunctional catalyst the enzyme is able to catalyze the condensation reaction without requiring very strong basic sites.[34,35,36]

In an analogous way a bifunctional organocatalyst containing a mild Lewis acid and a basic site at the adequate distance and orientation to stabilize the transition states may functionally mimic such biological catalysts. Thus, a series of organic molecules have been prepared in where the mild acid centre is constituted by a quaternary ammonium ion and the basic site consists of a secondary amine, separated from the acid site by one, two, or three carbon atoms. For comparative purposes analogous molecules with one or two amino basic groups or with only one acid site have also been prepared. As mentioned above, the Claisen-Schmidt condensation between aldehydes and ketones to produce *trans*-chalcones has been selected as test reaction, and the results for this reaction will be compared with those obtained for Knoevenagel condensation.[10]

3.1. Synthesis of chalcones

As outlined above, g*em*-diamine dipiperidinomethane tetrafluoroboric acid (**1**), dipiperidinoethane tetrafluoroboric acid (**2**) and dipiperidinopropane tetrafluoroboric acid (**3**) have been prepared. These molecules combine one basic and one mild acid sites separated by one, two or three carbon atoms, respectively, and with different rotating possibilities (Chart 1).

INSERT Chart 1

When the bifunctional *gem*-diamine dipiperidinomethane tetrafluoroboric acid **1** was used as catalyst for the Claisen-Schmidt condensation of benzaldehyde with acetophenone only the *trans*-chalcone (*cis*-chalcone was detected at the level of traces) was obtained with high yield (Table 1).

INSERT Table 1

Interestingly, typical secondary reactions of the base-catalyzed aldol condensation, such as self-condensation products derived from acetophenone or Cannizaro products derived from benzaldehyde, could not be detected with this catalyst under our experimental conditions. For comparative purposes the Claisen-Schmidt reaction between benzaldehyde and acetophenone was also carried out in the presence of three related bases such as *gem*-diamine **4**, piperidine **5**, and N-methylpiperidine **6** as catalysts under solventless conditions (see Chart 1 and Table 1). In this case, the highest yield of *trans*-chalcone was obtained using the bifunctional catalyst **1**, followed by the amines: piperidine **5** > dipiperidinomethane **4** > > > and N-methylpiperidine **6**.

Interestingly, when a basic (**6**) or acid (**7**) catalysts are used to run the reaction separately, the yield of *trans*-chalcone was 2 and 40 % respectively (see Table 1). However when a mixture of both catalysts (**6** and **7**) was used to run the reaction a very low yield of trans-chalcone (4%) was obtained. This fact evidences the importance of maintaining a proper distance between both functionalities, which in principle are incompatible, so that both can coexist on the same catalyst without deactivating each other.

The evolution of the yield of *trans*-chalcone with reaction time is depicted in Figure 1 for catalysts **1**, **4** and **5**.

INSERT Figure 1

The results indicate that the initial reaction rate for the bifunctional catalyst **1** is more than one order of magnitude higher than for the purely basic catalysts **4** and **5**. The superiority of the acid-base catalyst **1** with respect to the base *gem*-diamine **4** for the Claisen-Schmidt condensation cannot be merely due to differences in basicity, since the latter has stronger basicity than **1**. On the other hand, when the condensation reaction between benzaldehyde and acetophenone was carried out in the presence of a related Brönsted acid salt such as N-methylpiperidinium tetrafluoroborate **7** (Chart 1 and Table 1), the yield of *trans*-chalcone was much lower than that obtained with the bifunctional catalyst **1**, hence suggesting the existence of a cooperative role played by the basic and acid sites.

If the above hypothesis is accepted it can be postulated, in a first approximation, that the distance between the two active centres should be a crucial parameter for optimizing the activity and selectivity of the organocatalyst. In order to check this, two related bifunctional organocatalysts (**2** and **3** in Chart 1) with increasing separation between both active centres were prepared and used for the condensation of benzaldehyde with acetophenone. In both cases the condensation reaction hardly proceeds and the yield of *trans*-chalcone dramatically decreases when increasing the separation between the acid and basic sites (see Table 1).

These experimental results highlight the importance of structural parameters in a bifunctional organic catalyst, in where the two catalytic functions can jointly contribute to stabilize the transition state.

3.2 Molecular mechanism with bifunctional catalysts.

In order to explain at a molecular level the cooperative role played by the basic and acid sites in **1** and the poor results obtained with **2**, the mechanism of the Claisen-Schmidt condensation between acetophenone and benzaldehyde was theoretically investigated by means of DFT calculations. The energy profile is schematized in Figure 2, while the calculated adsorption, activation and reaction energies are summarized in Table 2, and the optimized geometries of all structures obtained with catalyst **1** are depicted in Figure 3.

INSERT Figure 2

INSERT Table 2

INSERT Figure 3

It can be seen in Figure 3 that the carbonyl group of acetophenone strongly interacts with the acid proton of the diamine, within a molecular orientation that also allows the interaction of a hydrogen atom of the methyl group with the lone pair of electrons of the basic N centre (Figure 3a, ketone). Then, in a concerted process the carbonyl group is protonated by the acid N-H of the quaternary ammonium at the same time that the basic N abstracts a hydrogen from the methyl group. The optimized geometry of the transition state (TS1, Figure 3b) clearly shows that the transfer of the

two hydrogen atoms, the change of the C-C bond from single to double, and the transformation of the carbonyl group into a hydroxyl occur simultaneously through an eight member cycle. The result of this elementary step, that implies the direct and cooperative participation of the acid and basic sites of the catalyst, is a molecule of 1-phenyl-ethenol interacting with the diamine (Figure 3c, labelled enol). In a second step, the carbonyl group of benzaldehyde interacts with the acid N-H centre displacing from this site the C=C double bond, while the stronger hydrogen bond between the hydroxyl group and the basic N of the catalyst is maintained (Figure 3d). The distance between the C atom of the aldehyde carbonyl group and the terminal C atom of the olefinic double bond in this complex is still large, 3.82 Å, but the relative orientation between the two molecules is the most adequate to interact without sterical repulsions between the aromatic rings. At this point, in a concerted process via transition state TS2 (Figure 3e), the new C-C bond is formed and two simultaneous hydrogen transfers involving the acid and basic sites of the catalyst occur leading to the condensation intermediate depicted in Figure 3f. In a third step, a water molecule is released from the intermediate yielding the desired *trans*-chalcone product.

We can see a functional parallelism between the condensation mechanism and the type-II enzymatic mechanisms of the aldolase. This is in the sense that the role of the divalent Zn^{2+} Lewis acid in the enzyme is assumed by the quaternary ammonium in organocatalyst **1**, while the abstraction of a proton by the residue Glu_{182} is assumed by the lone pair of electrons of the basic N centre in **1** (see step **I** in Scheme 2b). In a similar way, the activation of the carbonyl group by the residue Asp_{109} is carried out in our organocatalyst by the acid N-H group of the diamine **1**-enol intermediate (step **II** in Scheme 2b). A Claisen-Schmidt condensation intermediate is formed that will dehydrate to afford the *trans*-chalcone (steps **III** and **IV** in Scheme 2b).

3.3. Role of the distance between the acid and basic sites

To understand the influence of the separation between the acid and basic sites in the organocatalyst on its activity, the reaction mechanism was also studied on catalyst **2**, and the same elementary steps involving similar structures and energies were obtained. The values reported in Table 2, corresponding to the profile schematized in Figure 2, indicate that: a) acetophenone adsorption on both catalyst is exothermic by ~7 kcal/mol, b) the rate determining step is the keto-enol isomerization with activation energies between 14 and 19 kcal/mol and c) this first elementary step is endothermic. Co-adsorption of benzaldehyde is energetically favorable on the two diamines, and the activation energy for the condensation step through TS2 is higher when using catalyst **1**. Then, from the results obtained considering that the distance between the two sites in the bifunctional catalyst is the main factor responsible for the enhanced activity, one should conclude that catalyst **2** is better than **1**. However, the experimental results given in Table 1 clearly show that **2** is much less active for this reaction. Therefore a deeper analysis of the mechanism should be performed by further considering the initial adsorption and isomerization of acetophenone on the two catalysts, focusing our attention on the possibility of having different conformations that could influence the cooperation between the acid and basic sites.

3.4. Role of molecular orientation

There are at least two possible ways in which acetophenone can interact with catalyst **2**. In the structure depicted in Figure 4a, labelled ketone-**2a**, the acid and basic sites of the catalyst are pointing to the same region of space, while in the conformer shown in Figure 4b, labelled ketone-**2b**, the two sites are oriented in opposite directions.

INSERT Figure 4

Since the calculated mechanism requires a conformation of the catalyst in which the acid and basic sites point to the same region of space, we previously considered structure ketone-**2a** as the starting point for the theoretical study. However, structure ketone-**2b** is 3.7 kcal/mol more stable than ketone-**2a**, and therefore we have further investigated the relative stability of different conformers of catalysts **1** and **2**, both in their cationic form and interacting with the counter-anion BF_4^-. The results are depicted in Figure 5.

INSERT Figure 5

Two different conformations are obtained for catalyst **1**, as depicted in Figure 5a. In the most stable one, the acid N-H group is forming an angle of ~50º with the lone pair of the basic N, allowing the simultaneous interaction of acetophenone with the two sites, while the conformer with the two centres pointing in opposite directions is 5 kcal/mol less stable. The same relative stability is obtained when the diamine is interacting with the BF_4^- counter-anion, and therefore it can be concluded that the number of molecules of catalyst **1** with the adequate conformation will be high.

Rotation around the $-CH_2CH_2-$ bond that separates the acid and basic sites in catalyst **2** generates a larger number of conformers, but only the most stable ones are depicted in Figure 5b. In the cationic form, the most stable isomer corresponds to that with the adequate orientation to properly interact with the catalyst. In this structure, the flexibility of the $-CH_2CH_2-$ chain allows the formation of a strong hydrogen bond between the proton of the NH acid site and the basic N, indicated by the optimized NH--

N distance which is 1.94 Å. The conformer closest in energy, and not adequate for the reaction, is 9 kcal/mol less stable. However, when the counteranion is considered the interaction of the NH acid site with the BF_4^- counter-anion breaks the intramolecular hydrogen bridge in cationic **2** and, as a result, the order of stability changes considerably. Then, in the most realistic situation, the conformer with the adequate orientation of the acid and basic sites becomes 2 kcal/mol less stable than the structure with the two sites pointing in opposite directions. This order of stability is maintained, and the energy difference between them increases, after interaction with acetophenone. Therefore, the real situation under reaction conditions is that acetophenone interacts with **2** forming the complex depicted in Figure 4b, in which the relative orientation of the acid and basic sites does not allow the concerted keto-enol isomerization required in the first step of the mechanism. This picture explains the much lower activity of compound **2** for the Claisen-Schmidt condensation. Interestingly, in the case of the Knoevenagel condensation between benzaldehyde and a methylene active compound, the transition state for the rate determining step only involves the deprotonation of the methylene carbon by the basic center,[10] instead of the concerted process necessary for the Claisen-Schmidt condensation in where the carbonyl group is protonated by the acid site at the same time that the basic center abstracts a hydrogen atom from the methyl group (see Figure 6).

INSERT Figure 6

Therefore it appears that the relative orientation between the acid and base sites is much less determinant for the Knoevenagel than for the Claisen-Schmidt condensation. This explains two experimental observations: a) the activity of compound **2** in the

Knoevenagel condensation was found to be similar to that obtained with the purely basic dipiperidimethane catalyst (compound **4** in Chart 1),[10] and 2) the difference in activity between compounds **1** and **2** is much smaller for the Knoevenagel condensation than for the Claisen-Schmidt reaction. It can then be concluded that while the distance between the two sites (acid and base) in bifunctional organocatalysts is an important factor controlling activity in condensation reactions, in those cases in where the transition state for the rate determining step involves two simultaneous or concerted proton transfers, then the key parameter will be the geometrical conformation of the organocatalyst.

3.5. Influence of substrate

The influence of the substrate has been studied by reacting different *para* substituted benzaldehydes with acetophenone, and the results are reported in Table 3.

INSERT Table 3

The highest yields of *trans*-chalcones were obtained with electronwithdrawing groups such as $-NO_2$ or -Cl in *para* position of the benzaldehyde molecule, which may be due to the fact that electron withdrawing substituents activate the carbonyl group towards nucleophilic attack by means of either inductive and/or resonance effects.

3.6. Catalyst reusability

Catalyst **1** was designed in such a way that it has ionic liquid characteristics that allow its extraction from the reaction media by using the appropriate solvent. The reusability of bifunctional catalyst **1** was studied during the Claisen-Schmidt condensation. After extracting the products with diethyl ether, catalyst **1** was extracted

with dichloromethane from the crude left. After solvent elimination the recovered catalyst was reused in successive runs for the condensation of benzaldehyde and acetophenone and the results are depicted in Figure 7.

INSERT Figure 7

It is shown that catalyst **1** retained its high activity and selectivity after seven reaction cycles and the ^{1}H and ^{13}C NMR spectra of the recovered catalyst **1** showed that this organocatalyst was stable under these reaction conditions.

4. Conclusions

Class II aldolases, with a catalytic centre formed by a bifunctional system with basic and Lewis acid sites, have inspired the design of a bifunctional acid-base organocatalyst whose acid and basic functions are at an optimum distance and orientation. As it occurs with aldolase enzymes, this can be successfully applied for C-C bond forming reactions, and more specifically for the synthesis of valuable chemicals of biological and pharmaceutical importance, such as chalcones, through Claisen-Schmidt condensation reactions. The reactions are efficient and selective within a broad scope. This organocatalyst has been synthesized to present ionic liquid character in order to be recyclable. Therefore the organocatalyst presented here shows the advantages of the molecularly designed homogeneous catalysts with the recyclability of the heterogeneous.

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