Design of an organocatalyst for ion–molecule S_N2 reactions: A new solvent effect on the reaction rate predicted by ab initio calculations

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Abstract

Using ab initio calculations coupled with a continuum solvation model (PCM), it was shown that an organic molecule, 1,4-benzenedimethanol, is able to make two hydrogen bonds with anion–molecule S_N2 transition states. We have investigated the catalytic properties of this species for the S_N2 reaction between acetate ion and ethyl chloride in DMSO solution. Our calculations predicts an activation free energy barrier of 26.1 kcal mol^{-1} for the uncatalyzed mechanism and 20.2 kcal mol^{-1} for the catalyzed mechanism, a drop in the activation barrier in relation to free reactants by 5.9 kcal mol^{-1}. This organocatalyst is also able to catalyze E2 reactions and for the present system, the free energy barrier for the E2 mechanism drops by 5.3 kcal mol^{-1} due the action of the catalyst. Based on our theoretical data and even considering the formation of a complex between the acetate ion and the catalyst, we have estimated that the 1,4-benzenedimethanol mixed with the DMSO solvent should result in a powerful new solvent system, able to accelerate S_N2 reactions by a factor as large as 10^3 in relation to pure DMSO.
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Keywords: Organocatalysis; Ab initio calculation; Supramolecular chemistry; Nucleophilic substitution; Reaction mechanism; Esterification

1. Introduction

The importance of the solvent on chemical reactions is known since one century ago [1], but the dramatic influence of solvation on reaction kinetics has become particularly evident only after the development of gas-phase ion chemistry [2,3]. A notable example of the solvent effect on a chemical reaction is the interaction of the hydroxide ion with carboxylic esters [4–18]. Both theoretical [6] and experimental [13,18] studies show that the hydroxide ion reacts with the methyl formate in the gas-phase on almost every collision, and the main reaction products are $CO + H_2O \cdots ^-OCH_3$. The products generated from the $B_{AC}2$ and the S_N2 mechanisms, $HCOO^- + CH_3OH$, are also observed, but there are considerable differences with relation to the aqueous phase [5]. In this case, the reaction rate is smaller by many orders of magnitude and the $B_{AC}2$ mech-

anism is essentially the unique observed, a fact supported by both theoretical and experimental investigations.

During a long time, water was the main solvent used to perform ionic reactions in liquid phase. However, in the middle of the 20th century, the discovery of the rate acceleration of anion–molecule reactions in dipolar aprotic solvents in relation to the aqueous or protic solvents had a very important impact in organic chemistry [19]. This effect, due the formation of strong hydrogen bond between the anion and solvent molecules in protic solvents and a weaker interaction in dipolar aprotic solvents, is nowadays discussed in many textbooks of organic chemistry [20,21].

Although the rate acceleration due the transfer from protic to dipolar aprotic solvent is very important, no adequate parametrization of a continuum solvation model for dipolar aprotic solvents was available until recently. As a consequence, the only alternative for modeling this effect was the use of explicit solvation models coupled with free energy perturbation. However, Pliego and Riveros have recently reported a new parametrization of the polarizable continuum

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model (PCM) capable of a reliable modeling of the solvation in DMSO [22,23]. This parametrization was recently used to predict the rate acceleration effect for the reaction between hydroxide ion and ethyl acetate [4] and for the S_N2 reactions between acetate ion and the ethyl halides on the transfer from water to dimethyl sulfoxide (DMSO) solution [24]. In the last case, accurate activation free energy barriers were predicted in DMSO solution.

With the understanding of the factors that determine the reaction rate in liquid phase and the availability of reliable theoretical methods able to describe the solvent effect, it is possible to project organic molecules with defined catalytic activity. In this case, the catalysis is based on a carefully designed intermolecular interactions allowed to take place among the catalyst, the transition state and the solvent. With a selected stabilization of the transition state, the reaction time and the main product can be controlled. Indeed, the field of organocatalysis has received increased attention in the past few years [25–29]. As an example, Wittkopp and Schreiner [30] have investigated the catalysis of Diels–Alder reaction of dienes toward C=C conjugated to carbonyl groups by thioureas. These species are able to form two hydrogen bonds with carbonyl compounds and it was found that they are able to produce a rate acceleration by a factor of 8 when present at a proportion of 1% in relation to reactants.

In the present article, we have developed a new catalytic concept and designed an organic molecule with the required catalytic activity. However, different of recent studies, this catalyst is active on both S_N2 and E2 reactions in dipolar aprotic solvents. Since the development of the phase transfer catalysis [31], where the action of the catalyst is based on solubilization and formation of a free anion in an apolar solvent, no important advance has been reported on the rate acceleration of S_N2 reactions in organic solvents. In addition, this reaction kind plays a very important role in the process chemistry. Therefore, the present study can represent an important development of a new reaction medium for conducting S_N2 reactions.

2. The catalytic concept

Solvation in water and other protic solvents leads to a great stabilization of anions, mainly charge concentrated species. A consequence of this strong solute–solvent interaction is the decrease of the reactivity of the nucleophiles in these solvents. On the transfer from protic to dipolar aprotic solvents, it occurs a considerable decrease of the solvation of anions. As an example, recent experimental data [22] shows that the transfer of the hydroxide ion from aqueous to dimethyl sulfoxide solution has a free energy of $26\,kcal\,mol^{-1}$. On the other side, species with a wider dispersion of charge, such as the acetate ion, has a lower free energy of transfer, only $15\,kcal\,mol^{-1}$. Similarly, transition states of S_N2 reactions have a considerable dispersion of charge, resulting in a lower
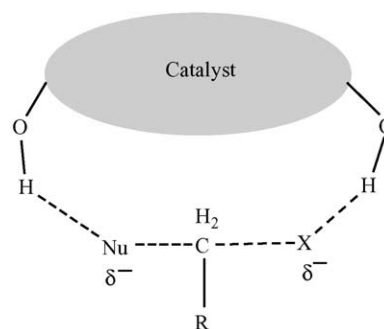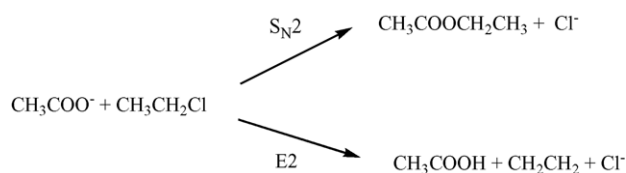

Scheme 1.

free energy of transfer. As a result, the activation free energy barrier decreases, accelerating the reaction rate.

In order to provide more acceleration of the S_N2 reactions in aprotic solvents, a possible approach would be to decrease the activation free energy barrier through stabilization of the transition state. This goal could be reached with the use of an additional molecule, able to form a complex with the transition state through strong hydrogen bonding. However, since the nucleophile could also to make hydrogen bond with the additional molecule, this catalytic effect would not be observed, unless the interaction with the transition state, a structure with dispersion of the negative charge, was stronger. A possible solution for this problem would be the use of a molecule able to form two hydrogen bonds in distant positions, as in the center of charge of the S_N2 transition states. Scheme 1 shows the idea of the action of the catalyst.

We have considered many possibilities and, in our theoretical research, we have found that the 1,4-benzenedimethanol, of formula I, has the required features.

I
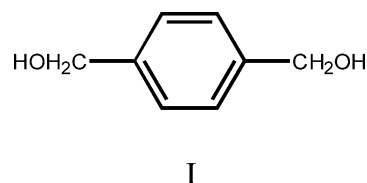
The two hydroxylic groups located across from the aromatic ring have the adequate distance to form two hydrogen bonds with a S_N2 transition state. In order to test this idea, we have investigated in this paper the reaction of the acetate ion with the ethyl chloride in DMSO solution, as well as the catalysis of this reaction by the 1,4-benzenedimethanol. Both of the S_N2 and the E2 pathways were studied (see Scheme 2).

Scheme 2.

3. Theoretical calculations

Geometry of every stationary point, minimum and transition state, was fully optimized at HF/6-31G(d) level of theory. Calculations of harmonic frequencies were performed in order to determine the nature of the stationary points and to obtain thermodynamic properties by standard statistical mechanics formulas. Although optimizations at MP2 level would be more accurate, this approach is very expensive for the present system. In a recent theoretical study of the S_N2 reaction between the acetate ion and the ethyl chloride [24], it was found that the geometry of the transition state obtained at MP2 level presents the O–C and C–X distances which are shorter by 0.1 Å than the values obtained at HF level. The respective activation barrier decreases by 1.5 kcal mol^{-1}. Thus, considering that our main objective in this work is to investigate the catalytic activity of the 1,4-benzenedimethanol, this error is acceptable. Nevertheless, in order to analyze the effect of electron correlation on the geometries and activation barriers, we have done some additional computations for some structures at B3LYP/6-31G(d) level.

In order to obtain accurate electronic energies, it is important to make single point calculations using a higher level of theory. However, due the size of the present system, we have used an ONIOM like approximation [32,33]. The reactants (acetate plus ethyl chloride, named R) were chosen as the model system and for these we have made single point calculations at MP2/6-31 + G(d), CCSD(T)/6-31 + G(d) and MP2/6-311 + G(2df,2p) levels of theory. In addition, additivity approximation was used to obtain an effective CCSD(T)/6-311 + G(2df,2p) calculation for R. In this method, increasing the 6-31 + G(d) basis set to 6-311 + G(2df,2p) one either using the MP2 or the more accurate CCSD(T) method is considered to have the same effect on the energy [34]. For the real system, composed of the reactants plus the catalyst (named R + C), we have made single point calculations at MP2/6-31 + G(d) level. Thus, the energy of the full system was calculated as:

$$E(R + C : CCSD(T)/EB) \approx E(R + C : MP2/6 - 31 + G(d)) + [E(R : CCSD(T)/EB) - E(R : MP2/6 - 31 + G(d))]$$

where EB corresponds to the 6-311 + G(2df,2p) basis set. Using the ONIOM notation, the present calculations can be written as ONIOM[CCSD(T)/6-311 + G(2df,2p):MP2/6-31 + G(d)]. Thus, the reactive part was described at CCSD(T)/6-311 + G(2df,2p) level of theory while the interaction of the catalyst with the transition state was described at MP2/6-31 + G(d) level. This is a very reliable methodology.

The solvent effect was included through the polarizable continuum model (PCM) using the IEF routines [35–39] and the HF/6-31 + G(d) wave function. We have studied the reaction in DMSO solution using the Pliego and Riveros

parametrization of the PCM model [23]. It was recently shown that this parametrization is able to predict pK_a of organic acids in DMSO solution with an average error of only 2.2 pK_a units [40]. An independent study by Liu and co-workers has found a similar performance [41]. Further, in a recent application of this method for modeling S_N2 reactions between acetate ion and ethyl halides (Cl, Br, I) in DMSO solution [24], the respective activation free energies were predicted with an average error lower than 2 kcal mol^{-1}. Thus, this parametrization is very reliable for describing the electrostatic solvation.

All ab initio gas-phase calculations were done with the Gaussian 98 program system [42] and for the PCM calculations, we have used the Gamess program system [43]. In addition, it was used the standard state of 1 mol L^{-1} for the reported thermodynamics data.

4. Results and discussion

The main gas-phase optimized structures studied in this work are presented in Fig. 1 and the respective activation and reaction thermodynamic properties relative to free reactants are in Table 1. Our calculations indicated that the acetate ion reacts with the ethyl chloride via the S_N2 mechanism (TS1) with an activation free energy barrier of 26.1 kcal mol^{-1} in DMSO solution. This value is close to the $\Delta G^{\ddagger}$ of 24.9 kcal mol^{-1} that was obtained in a previous work [24] at MP4/CEP-31 + G(d)//MP2/CEP-31 + G(d) level. For comparison, a barrier of 22.3 kcal mol^{-1} can be obtained from experimental data [24]. The deviation of 3.8 kcal mol^{-1} points out the good quality of our calculations, which could be improved by geometry optimization at MP2 level. Furthermore, the nonelectrostatic contribution to the solvation free energy, not included in this study, should decrease the activation barrier due to the packing effects and to provide a more reliable $\Delta G^{\ddagger}$.

In addition to the S_N2 pathway, we have also investigated the parallel E2 mechanism, corresponding to the TS2 structure in Fig. 1. It can be observed that the acetate ion abstracts the proton while the chloride ion leaves the forming CH_2CH_2 product. Our calculations predict an activation free energy barrier of 31.9 kcal mol^{-1}, indicating that this pathway is not important for this system. This finding is in agreement with the observation that primary halides usually does not react through the elimination mechanism [20], unless a very strong base is present. In fact, the large difference of 5.8 kcal mol^{-1} between the S_N2 and E2 pathways point out that even traces of the E2 reaction products should not be observed.

The reaction through the catalyzed mechanism begins with the formation of the acetate–catalyst complex (Cat$\cdots$AcO$^-$). During the design of the catalyst, our objective was to create a structure that would not form two hydrogen bonds with the nucleophile, because this structural feature should decreases the catalytic activity. Although the acetate ion forms two hydrogen bonds, it can be noted (Fig. 1) that the catalyst
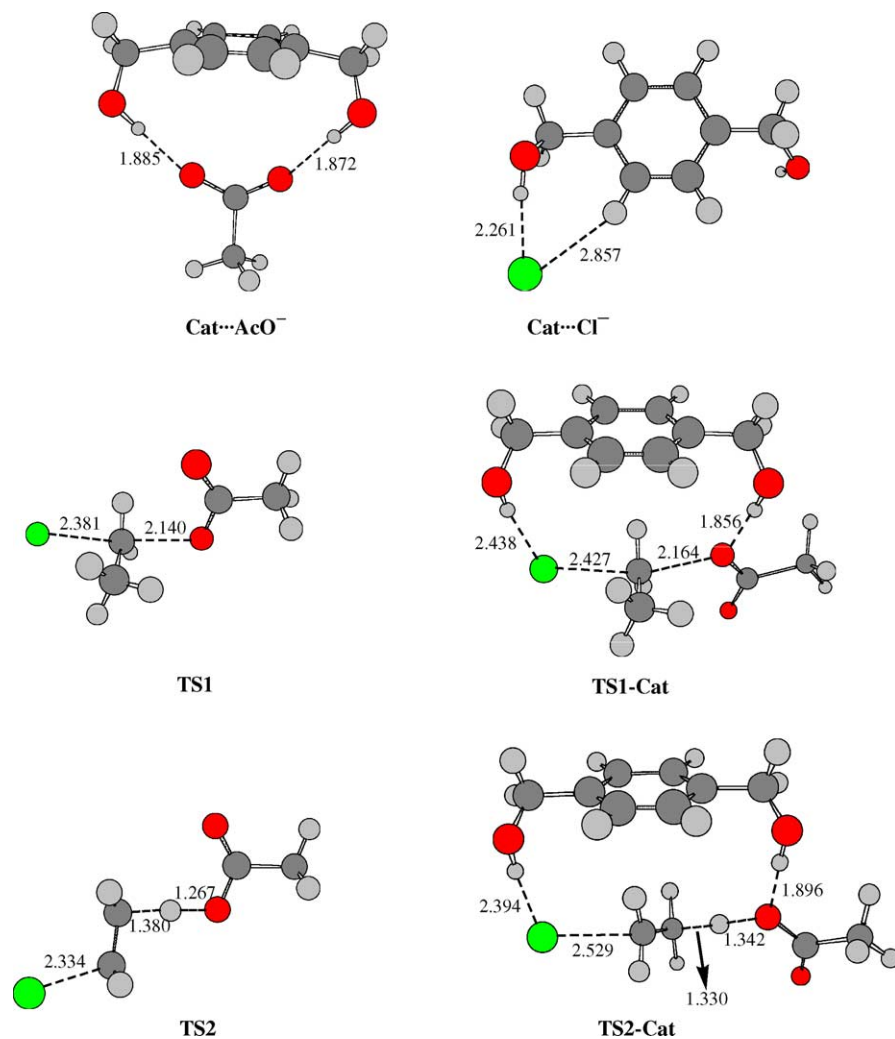
Fig. 1. Transition states and ion–molecule complexes.

is considerably deformed in order to form the two hydrogen bonds and this fact decreases the stability of the complex. More important is the fact that the center of charge of the bound acetate ion is not available to interact with the solvent. As a consequence, the medium makes a very positive con-

tribution to the formation of the complex (18.7 kcal mol^{-1}) resulting in a free energy of formation in DMSO solution of only -1.6 kcal mol^{-1}. We have also investigated another possible complex, where the interaction between the acetate ion and the catalyst takes place through the hydrogen of

Table 1
Thermodynamic properties in relation to free reactants[a]

Species	MP2/6-31 + G(d)	MP2/6-31 + G(d)[b]	MP2/ext[c]	CC/6-31 + G(d)[d]	CC/ext[e]	ΔH_g	ΔS_g	ΔG_g	$\Delta\Delta G_{solv}$	ΔG_{sol}
Cat···AcO⁻ + EtCl	−30.19	−30.81				−28.06	−26.22	−20.24	18.68	−1.56
TS1	5.64	4.85	5.60	2.52	2.48	3.72	−24.82	11.11	14.96	26.07
TS1-cat	−23.02	−25.40	−22.72	−26.36	−26.07	−22.48	−58.58	−5.02	25.20	20.18
Cat···Cl⁻ + AcOEt	−36.61					−33.17	−29.05	−24.51	12.03	−12.48
Cat + AcOEt + Cl⁻	−13.81		−13.08	−14.90	−14.16	−11.72	−15.06	−7.24	−2.28	−9.52
TS2	16.60		12.43	16.05	11.88	9.39	−21.89	15.91	16.01	31.92
TS2-cat	−10.11		−13.26	−11.12	−14.27	−14.42	−55.30	2.07	24.69	26.76
AcOH + CH$_2$CH$_2$ + Cl⁻	9.00		6.93	6.35	4.28	3.33	10.79	0.11	−3.95	−3.84

[a] Standard state of 1 mol L^{-1}, 298.15 K. Units of kcal mol^{-1}. Symmetry fctors included. Geometries and frequencies at HF/6-31G(d) level.

[b] Using B3LYP/6-31G(d) geometries.

[c] This corresponds to ONIOM[MP2/6-311 + G(2df,2p):MP2/6-31 + G(d)].

[d] This corresponds to ONIOM[CCSD(T)/6-31 + G(d):MP2/6-31 + G(d)].

[e] This corresponds to ONIOM[CCSD(T)/6-311 + G(2df,2p):MP2/6-31 + G(d)] using additivity approximation for the small system.

the OH group and the hydrogen from the aromatic ring. In this case, the free energy of formation in DMSO solution is $-0.7\,kcal\,mol^{-1}$. Thus, this complex is not important in the present study and it will not be considered anymore.

Through the catalyzed pathway, the complex can interacts with ethyl chloride, leading to the transition state TS1-Cat. In agreement with our design, the catalyst forms two hydrogen bonds with the S_N2 transition state and its structure undergoes to a small modification in relation to the uncatalyzed pathway. However, this interaction is sufficiently strong to produce a notable stabilization of this species in relation to the uncatalyzed reaction. Taken the gas-phase $\Delta G^{\ddagger}$ of the uncatalyzed and catalyzed reaction, we can calculate that the catalyst decreases the barrier by $16.1\,kcal\,mol^{-1}$. On the other hand, the solvent effect is larger for the catalyzed pathway, increasing the barrier by $15.0\,kcal\,mol^{-1}$ for the uncatalyzed mechanism and $25.2\,kcal\,mol^{-1}$ for the catalyzed mechanism. As a consequence, the $\Delta G^{\ddagger}$ barrier of the S_N2 pathway in solution decreases by only $5.9\,kcal\,mol^{-1}$ ($\Delta G^{\ddagger} = 20.2\,kcal\,mol^{-1}$) due the action of the catalyst.

The catalyzed S_N2 reaction leads to ethyl acetate (AcOEt) plus the catalyst–chloride ion complex (cat$\cdots$Cl$^-$). The last species has a dissociation free energy of $3.0\,kcal\,mol^{-1}$, indicating that the chloride ion has a stronger interaction with the catalyst than the acetate ion in DMSO solution. In the gas-phase, the reverse is observed. It can be explained if we observe that the chloride ion into the cat$\cdots$Cl$^-$ complex is exposed for interacting with the solvent, while the center of charge of the acetate ion is oriented toward the catalyst. Thus, the solvent stabilizes the cat$\cdots$Cl$^-$ complex more than the cat$\cdots$AcO$^-$ one.

We have also investigated the elimination pathway (E2 mechanism), because of the possibility of the catalyst to be active on this transition state. Indeed, the $-CH_2OH$ moiety has a reasonable flexibility and as a consequence, the catalyst could be able to interact with both S_N2 and E2 transition states. We have found the TS2-Cat structure, which corresponds to the catalyzed elimination step. This structure confirms that the catalyst has an adequate interaction with the E2 transition state. The activation free energy barrier from the free reactants is $26.8\,kcal\,mol^{-1}$, a decrease by $5.1\,kcal\,mol^{-1}$ in relation to the uncatalyzed mechanism. Thus, it is evident that the 1,4-benzenedimethanol is also able to catalyze E2 reactions and its catalytic power for both S_N2 and E2 pathways are close. However, considering that the barrier for the catalyzed E2 pathway is $6.6\,kcal\,mol^{-1}$ higher than the S_N2 pathway, the elimination reaction will not take place for this system.

Because the geometries calculated in this study were obtained at Hartree–Fock level, we have done additional computations at MP2/6-31 + G(d)//B3LYP/6-31G(d) level of theory for the reactants, TS1 and TS1-cat in order to analyze the importance of electron correlation to the geometries and its effect on the activation barriers in relation to the MP2/6-31 + G(d)//HF/6-31G(d) level. For the pathway through TS1, the gas phase barrier drops by $0.8\,kcal\,mol^{-1}$, while for the TS1-cat, the barrier drops by $2.4\,kcal\,mol^{-1}$. However, considering that the cat$\cdots$AcO$^-$ complex is also stabilized by $0.6\,kcal\,mol^{-1}$, the effective stabilization of the TS1-cat in relation to TS1 is only $1.0\,kcal\,mol^{-1}$. Thus, use of the B3LYP geometry produces a small stabilization of the catalyzed pathway.

A general view of the free energy profile of this reaction system is shown in Fig. 2.

Although the 1,4-benzenedimethanol catalyst decreases the activation barrier for the S_N2 pathway by $5.9\,kcal\,mol^{-1}$,
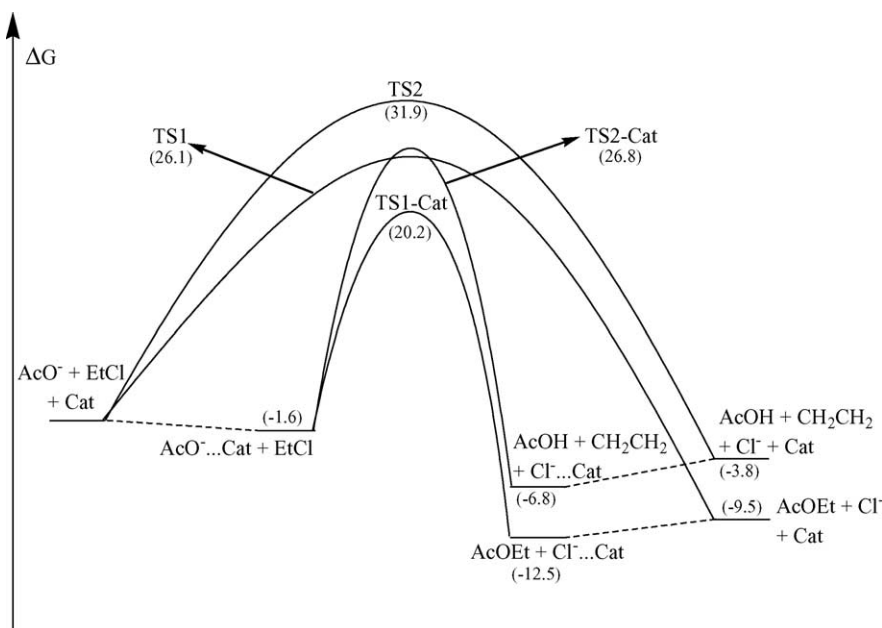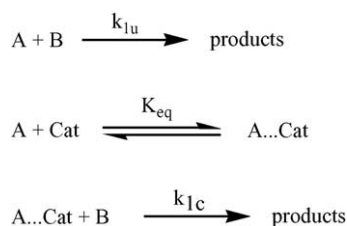

Fig. 2. Free energy profile of the reaction between AcO$^-$ and EtCl catalyzed by 1,4-benzenedimethanol in DMSO solution.

Scheme 3.

it also forms a complex with the acetate ion and this interaction decreases the catalytic activity. Considering Fig. 2, we can make a rough evaluation of the rate acceleration effect. Taking the $AcO^-\cdots cat$ complex as reference, the effective barrier for the catalyzed reaction would be $21.7\,kcal\,mol^{-1}$, indicating a decreasing of $4.4\,kcal\,mol^{-1}$ in relation to uncatalyzed mechanism. In order to make a correct estimate of the catalyzed reaction rate, it is needed to write a kinetic model. Scheme 3 shows the model that we have analyzed.

A, B and cat correspond to acetate, ethyl chloride and the catalyst, respectively. Based on Table 1 and Fig. 2, the rate and equilibrium constants can be evaluated as $k_{1u} = 4.8 \times 10^{-7}\,L\,mol^{-1}\,s^{-1}$, $K_{eq} = 14\,mol\,L^{-1}$ and $k_{1c} = 7.2 \times 10^{-4}\,L\,mol^{-1}\,s^{-1}$. Considering C_A, C_B and C_{cat} the total concentration of each species, $C_A \gg C_{cat}$ and $C_A > 0.1\,mol\,L^{-1}$, the catalyzed reaction rate can be written as:

$$rate_{cat} = k_{1c} C_{cat} C_B \qquad (1)$$

and

$$rate_{uncat} = k_{1u} C_A C_B \qquad (2)$$

Thus, the relative reaction rate will be:

$$\frac{rate_{cat}}{rate_{uncat}} = 1500 \frac{C_{cat}}{C_A} \qquad (3)$$

Based on Eq. (3), if the concentration of the catalyst was 10% of the concentration of the acetate ion, the reaction rate would increase by a factor of 150. This is a very significant rate acceleration effect.

The 1,4-benzenedimethanol could also be used as a cosolvent, mixed with DMSO. In this case, the rate acceleration would be much more accentuated. Indeed, considering the kinetic model of scheme III, and taking $C_{cat} \gg C_A$ and $C_{cat} > 0.1\,mol\,L^{-1}$, we can write:

$$rate_{cat} = k_{1c} C_A C_B \qquad (4)$$

Eq. (4) indicates that practically all acetate ions would be bound to the catalyst. In this case, the relation between the catalyzed and uncatalyzed reaction rate would be:

$$\frac{rate_{cat}}{rate_{uncat}} = \frac{k_{1c}}{k_{1u}} = 1500 \qquad (5)$$

This is a substantial rate acceleration and point out that a mixture of DMSO with 1,4-benzenedimethanol could be

a new and powerful solvent system. In our opinion, a concentration at $1\,mol\,L^{-1}$ of 1,4-benzenedimethanol in DMSO would be an adequate proportion. This higher concentration has another advantage: the formation of the complex between the catalyst and the chloride ion would not decrease the reaction rate. Rather, using catalytic quantities, the chloride ion released in the reaction would contribute to inhibit the catalysis through bound to the catalyst. In excess, the catalytic activity would not be modified.

Other dipolar aprotic solvents could be used to perform the reaction. In fact, analyzing the $\Delta\Delta G_{solv}$ of Table 1, it can be observed that the most positive value occurs for the TS1–cat structure. Thus, on going to less solvating solvents such as dimethylformamide or acetonitrile, the reaction rate should increase. However, other factors, as the formation of ion pairs between the nucleophile and the respective cation, must be analyzed before having a definitive conclusion. By the way, the present results indicate that the 1,4-benzenedimethanol can be the basic structure of a new class of organocatalysts, capable of catalyzing S_N2 and E2 reactions. In our knowledge, there are not similar catalyst reported in the literature. Structural modifications in this molecule could create new and more powerful organocatalytic species. Research in this direction is undergoing.

5. Conclusion

The present theoretical study shows that 1,4-benzenedimethanol is an organocatalyst for S_N2 and E2 reactions, and its activity is based on the formation of two strong hydrogen bonds with these transition states. Our calculations predicts that in the reaction of acetate ion with primary chlorides, where the S_N2 pathway dominates, using 10 mol% of the catalyst in relation to acetate ion produces a rate acceleration by a factor of 150. When used in excess, as a cosolvent added to DMSO, the rate constant increases by a factor of 1500, a substantial catalytic effect.

Acknowledgment

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