Regioselective organocatalysis: a theoretical prediction of the selective rate acceleration of the S_N2 reaction between an acetate ion and primary alkyl chlorides in DMSO solution

Josefredo R. Pliego, Jr.*

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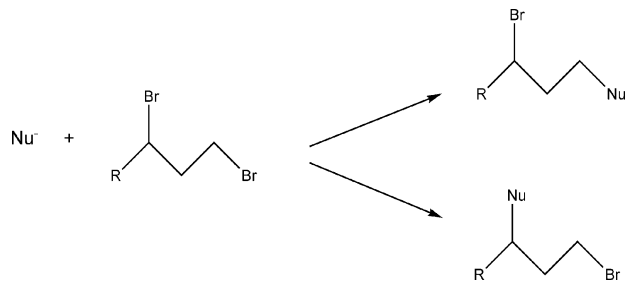
High level *ab initio* calculations, including the solvent effect through a continuum solvation model, predict that 1,4-benzenedimethanol is able to catalyse the S_N2 reaction between an acetate ion and primary alkyl chlorides in dimethyl sulfoxide solution. The catalysis takes place through two selective hydrogen bonds to the transition state. However, for secondary alkyl chlorides the catalysis is not effective due to steric repulsion and desolvation. This effect induces regioselective control of S_N2 esterification reactions.

Introduction

The rate of bimolecular nucleophilic substitution (S_N2) reactions is changed by different factors.[1] In the case of alkyl halides, it is known that the reactivity order (primary > secondary carbon) is usually followed. However, these differences may not be large, resulting in substitution products on primary and secondary carbons when a polyhalogenated molecule is reacting. Scheme 1 presents the problem.



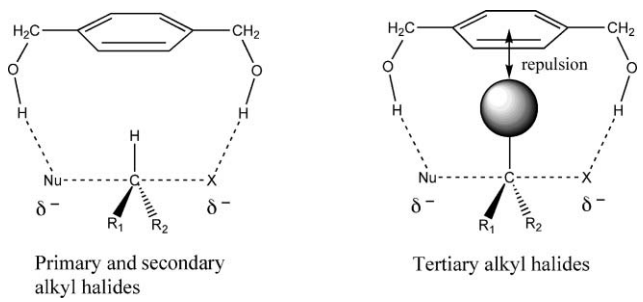
Scheme 1

If R is an alkyl group, nucleophilic attack on the primary carbon will be the main reaction, but some substitution on the secondary carbon can take place. Otherwise, if R is an activating group, such as phenyl or vinyl, the attack on this position could be the most important pathway. The worst situation occurs when both pathways are equally significant. For organic synthesis applications, this diversity of products is undesirable, leading to generation of waste. The most elegant way to resolve this problem would be to use catalysis. Thus, regioselective control of chemical reactions could be an important tool for building complex molecules.

In the past few years, the use of organic molecules as catalysts, named organocatalysis, has been emerging as a powerful method for accelerating and controlling chemical reactions.[2–17] In this way, we have recently used high level *ab initio* calculations to show that 1,4-benzenedimethanol is an organocatalyst for ion–molecule S_N2 reactions of the kind:[18]

$$R_1COO^- + R_2\text{–}Cl \rightarrow R_1COOR_2 + Cl^-$$

The catalysis is based on the formation of two hydrogen bonds between the catalyst and the center of charge of the S_N2 transition state as presented in Scheme 2. Although that study has considered only the reaction with a primary alkyl chloride (ethyl chloride), an analysis of Scheme 2 shows that reactions with tertiary alkyl chlorides should not be catalysed due to steric repulsion.



Scheme 2

While this analysis shows that the transition states involving tertiary alkyl halides reacting with any nucleophile should not have a favorable interaction with 1,4-benzenedimethanol, it is less clear how the nature of the nucleophile could lead to a possible selectivity for the reaction with a primary or secondary alkyl halide (Scheme 1). It is reported in this work that the S_N2 reaction of the acetate ion with a primary alkyl chloride is selectively catalysed by 1,4-benzenedimethanol and for the secondary alkyl chloride the catalysis is less important. The system investigated is the reaction of the acetate ion with propyl chloride and with isopropyl chloride in dimethyl sulfoxide solution, both reactions catalysed by 1,4-benzenedimethanol (BDM).

Departamento de Química, Universidade Federal de Santa Catarina, 88040-900, Florianópolis, SC, Brazil. E-mail: josef@qmc.ufsc.br

Calculations

The *ab initio* calculations were performed at HF/6-31G(d) level for gas-phase geometry optimization and harmonic frequency calculations. Single point energy calculations were done at the ONIOM[CCSD(T)/6-311 + G(2df,2p): MP2/6-31 + G(d)] level of theory,[19] the same method as used in our previous work.[18] The solvent effect was included through single point calculations on the gas-phase optimized structures using the polarizable continuum model (PCM)[20–22] and the Pliego and Riveros parametrization.[23–25] Previous studies have shown the high reliability of the present method for DMSO solution[25–28] and even for protic solvents, where specific interactions may be important in many cases,[29,30] the continuum model provides a good description of the solvent effect.[31–33] All of the *ab initio* calculations were done with the Gaussian 98[34] package while the PCM computations were performed with the Gamess program.[35]

Results and discussion

The optimized transition state structures are presented in Fig. 1, and Table 1 shows the activation thermodynamic properties. For the uncatalysed reaction, the free energy barrier for the propyl chloride reaction in the gas phase is 9.9 kcal mol^{-1} and the solvent increases the barrier by 16.5 kcal mol^{-1}, resulting in a $\Delta G_{sol}^{\ddagger}$ of 26.4 kcal mol^{-1}. This value is close to the ethyl chloride reaction previously reported. For the secondary chloride, isopropyl chloride, the gas phase barrier is 13.8 kcal mol^{-1}. Thus, we can notice a high selectivity of the reaction in the gas phase when comparing primary and secondary alkyl chloride reactions. Indeed, the barrier increases by 3.9 kcal mol^{-1} on going from the primary to the secondary chloride. However, inclusion of the solvent effect increases the free energy barrier for the isopropyl chloride reaction by only 13.6 kcal mol^{-1}, resulting in a final $\Delta G_{sol}^{\ddagger}$ of 27.4 kcal mol^{-1}. Thus, the solvent eliminates the selectivity for the reaction and in solution the barriers differ by only 1.0 kcal mol^{-1}. We can make a comparison with the average reactivity scale.[1] This scale states that the general reactivity order between ethyl and isopropyl substrates is around 1.6 kcal mol^{-1}, very close to our theoretical prediction value of 1.0 kcal mol^{-1}. A similar effect was reported by Vayner *et al.*[36] for the S_N2 reaction of ethyl chloride and neopentyl chloride with the chloride ion in gas phase and in DMSO solution. In these cases, while the difference in the activation free energy is 7.2 kcal mol^{-1} in the gas phase, it becomes 6.9 kcal mol^{-1} in the DMSO solution. The decrease of 0.3 kcal mol^{-1} is much smaller than the 2.9 kcal mol^{-1} observed in our present study, but the same effect takes place.

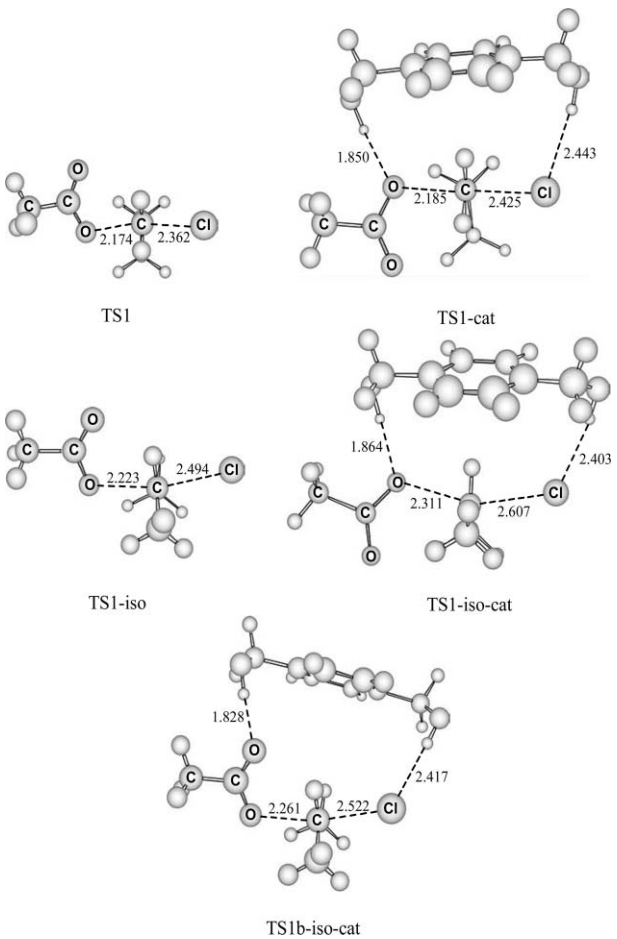


Fig. 1 Optimized transition state structures.

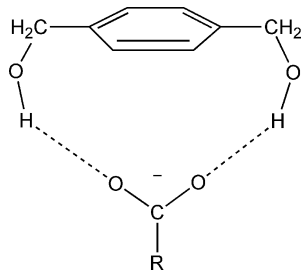
Table 1 Activation properties for the S_N2 reaction $AcO^- + R–X$[a]

	$\Delta E^{\ddagger}$[b]	$\Delta G_g^{\ddagger}$[c]	$\Delta\Delta G_{solv}^{\ddagger}$[d]	$\Delta G_{sol}^{\ddagger}$[e]
TS1	0.8	9.9	16.5	26.4
TS1-cat	−28.0	−6.3	26.4	20.1 (21.7)
TS1-iso	5.2	13.8	13.6	27.4
TS1-iso-cat	−22.5	−1.3	26.5	25.2 (26.8)
TS1b-iso-cat	−21.7	−1.8	26.3	24.5 (26.1)

[a] Units of kcal/mol. Standard state of 1 mol L^{-1}, 298 K, DMSO solution. [b] Energies obtained at ONIOM[CCSD(T)/6-311 + G(2df,2p): MP2/6-31 + G(d)] level using HF/6-31G(d) geometries and frequencies. [c] Gas-phase activation free energy. [d] Solvation contribution to the activation free energy. [e] Solution-phase activation free energy from free reactants. The values in parentheses correspond to the activation free energy taking into account the catalyst–acetate ion complex formation.

This interesting lower selectivity in the liquid phase requires a careful examination. The answer to the problem is shown in Fig. 1. We can observe that the forming and breaking O–C and C–Cl bonds are shorter for the TS1 structure and longer for the TS1-iso structure. As a consequence, the solvent has a greater interaction with the TS1-iso transition state, because this species has more charge concentration on the nucleophilic fragments and it is more exposed to interact with the solvent. The final effect is a decrease of the gas phase selectivity.

The BDM catalyst is able to complex with both transition states (Fig. 1, TS1-cat and TS1-iso-cat) and the gas phase catalysed free energy barrier is 16.2 kcal mol^{-1} and 15.2 kcal mol^{-1} more negative than the uncatalysed mechanism for both propyl chloride and isopropyl chloride, respectively. Thus, the catalyst increases the gas phase selectivity and the final difference in the activation free energy is 5 kcal mol^{-1}. Unexpectedly, the solvent effect is very close for both transition states, increasing the barrier by 26.4 kcal mol^{-1} and 26.5 kcal mol^{-1}. The resulting $\Delta G_{sol}^{\ddagger}$ are 20.1 kcal mol^{-1} and 25.2 kcal mol^{-1} for propyl chloride and isopropyl chloride, respectively. Because the catalyst can form a complex with the acetate ion ($\Delta G_{sol} = -1.6$ kcal mol^{-1}, Scheme 3), the observed



Scheme 3

barriers will be 21.7 kcal mol^{-1} and 26.8 kcal mol^{-1} (values in parentheses, Table 1). Therefore, the high selectivity lost in the uncatalysed solution phase reaction is recovered in the catalysed reaction. Furthermore, while the catalytic activity is important for the propyl chloride reaction, decreasing the free energy barrier by 4.7 kcal mol^{-1}, it is small for the isopropyl chloride reaction, having a drop in the barrier of only 0.6 kcal mol^{-1}.

Why is there no catalytic activity for the reaction involving the secondary chloride? Again, Fig. 1 can answer the question. The TS1-iso-cat structure shows that both the steric repulsion between the oxygen of the acetate moiety and the methyl groups and the reduced exposition of the center of negative charge to the solvent produce this effect. The steric effect can be observed in the gas phase values, where the transition state for the isopropyl chloride reaction is less stabilized by 1 kcal mol^{-1} in the catalysis. The remaining difference arises from the interaction with the solvent. Thus, the more effective solvation of the TS1-iso transition state is lost in the TS1-iso-cat structure because there is less exposition of the center of negative charge to interact with the solvent due to the methyl groups of the isopropyl moiety.

However, another catalysed transition state with less steric repulsion is possible and corresponds to the structure TS1b-iso-cat. In this case, the nucleophilic attack takes place by the oxygen below while the hydrogen bonding to the catalyst occurs through the oxygen above. This structure alleviates the steric repulsion observed in the structure TS1-iso-cat but the interaction with the catalyst decreases. Although this structure is more stable than the TS1-iso-cat one, having a $\Delta G^{\ddagger} = 24.5$ kcal mol^{-1}, the observable activation free energy barrier is 26.1 kcal mol^{-1}, only 1.3 kcal mol^{-1} below that of the uncatalysed mechanism. Therefore, the catalytic effect for the secondary carbon reaction is small.

The possibility of controlling which reactive site will undergo nucleophilic attack is very important to achieve high yields and to have less secondary product generation. The present study predicts that BDM induces high selectivity in the S_N2 reactions involving carboxylate ions and polyhalogenated molecules. BDM catalyses the reaction on the primary carbon position while it is almost inactive on the secondary carbon, resulting in essentially 100% substitution on the primary carbon. Chemoselectivity of esterification reactions is a topic of current interest.[37] In the present work, it is predicted that regioselectivity of the esterification by an S_N2 reaction is achieved through organocatalysis.

Conclusion

The present high level theoretical study predicts that S_N2 reactions involving carboxylate ions and primary alkyl chlorides in DMSO solution are catalysed by 1,4-benzenedimethanol, but in the case of secondary alkyl chlorides the catalysis is not effective. As a consequence, polyhalogenated molecules would react selectively with carboxylate ions at the primary carbon position in the presence of 1,4-benzenedimethanol.

Acknowledgements

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