



A comprehensive theoretical investigation of the transition states and a proposed kinetic model for the cinchoninium ion asymmetric phase-transfer catalyzed alkylation reaction



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ABSTRACT

The discovered that the cinchoninium ion could promote a highly enantioselective alkylation of an indanone enolate via phase-transfer catalysis was a breakthrough in the area asymmetric organocatalysis. However, only recently the mechanism of asymmetric induction was unraveled by theoretical calculations. It was found the process takes place through cooperative catalysis with a key role of the cinchoninium hydroxyl group. In this work, we have done a more detailed investigation of the possible transition states, reporting twenty-four structures. More reliable calculations at MP2 level was applied to the most important species and we have observed that dispersion forces play a very important role to selectively stabilize the critical transition state leading to the main enantiomer. The possible partition equilibria of several species have also been considered and a kinetic model was proposed. We have found the formation of a dimer of the cinchoninium ion takes place and this behavior leads to fractional kinetic order in the catalyst concentration. The theoretical overall kinetics is in very good agreement with the experimental data, with an effective activation free energy barrier deviating by only 1.2 kcal mol⁻¹ from the experimentally observed value. This study provides a very detailed picture at molecular level for this reaction system at first time.

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1. Introduction

The discovered that bulk cations like tetrabutylammonium could work as a catalyst via transport of anions from water to apolar organic phase has led to the birth of the phase-transfer catalysis [1–4]. Because in apolar solvents ions exist like ion pairs, the possibility of using an asymmetric cation to induce formation of a chiral product has begun to be explored [5]. The first successful asymmetric phase-transfer catalyzed reaction reported was the enantioselective alkylation of indanone using the cinchoninium ion as catalyst (Scheme 1) [6]. This reaction has become a classical example of asymmetric organocatalysis. In the seminal paper of Dolling et al., those authors have proposed a mechanism for asymmetric induction based on tight ion pair formation between the indanone anion and the cinchoninium ion as presented in Scheme 2.

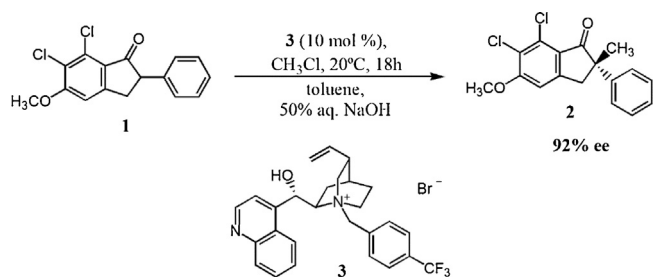
This tight ion pair would prevent the attack of the methyl chloride on one side, leading to asymmetric reaction.

On the years, the Dolling et al. idea of asymmetric induction has been used to explain the selectivity. However, a very recent theoretical study [7] using density functional theory has shown that the most stable ion pair involving the indanone anion and the cinchoninium cation is different from that proposed by Dolling et al. It was observed that the close proximity between the carbonyl oxygen of indanone with the nitrogen of cinchoninium leads to favorable electrostatic interaction and the indanone moiety rotate relative to hydrogen bond in order to be able to stay close to center of positive charge of the cinchoninium ion (Scheme 2). In addition, the ion pair is very flexible and there is several minima energy structures. Because the steric impediment for attacking of the methyl chloride is not present in this structure, the origin of selectivity is due the stabilization of the leaving chloride anion in the transition state (Scheme 2). It is interesting to notice that this kind of stabilization of anionic S_N2 transition states has been proposed some years ago based on theoretical calculations [8–10]. In the present, there is an increased interest in this cooperative mode of catalysis [11–13].

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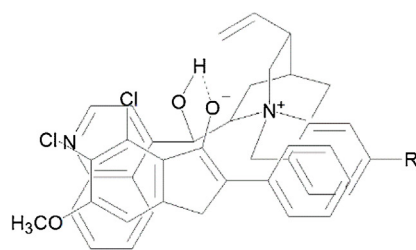
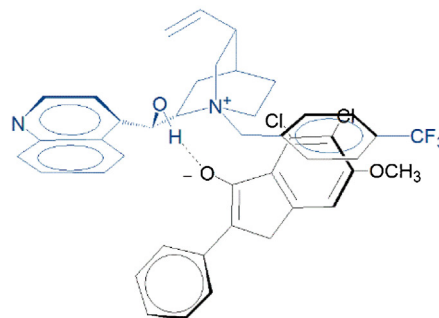


Scheme 1. Alkylation of indanone.

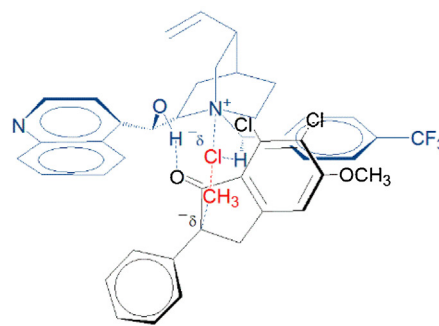
The area of phase transfer catalysis remains very active with new important developments [14–21]. The molecular level understand of the catalyst-substrate interaction, partition equilibria, formed species and details of the interface process is expected to play a very important role in the design of new catalysts [22–28]. In special, theoretical calculations provide unique insights in the reaction mechanisms and play a critical role in the investigation of organocatalyzed reactions [29–33]. However, reactions involving large tetraalkylammonium cations have been studied only recently, once it involves large and flexible structures [26,34,35]. Our first report on the phase-transfer catalyzed alkylation of indanone [7] has paid attention to the enantioselective aspects of the process, analyzing the structures of the main transition states. Nevertheless, there is yet several questions that deserves be answered for this classical reaction [36]. The first question is related to twelve indanone anion-catalyst complexes, which can lead to twenty-four transition states. We have analyzed only four transition states in our preliminary communication and it is possible that other structures can be important too. The second question is related to the formation of a dimer of the catalyst and the reaction order around 0.5 in the catalyst. This point needs be more examined. The third question is the several partition equilibria involving the chemical species present in the system. A careful analysis of these aspects is warranted in order to obtain a reliable theoretical description of the system. The fourth point is the observed kinetics. The reaction time is around 1 h and we can make a rough estimate of the overall activation free energy barrier as being around 22 kcal mol⁻¹ [37]. The barrier calculated in the previous work is 26 kcal mol⁻¹, and considering that the several equilibria could lead to higher observed barrier, we believe this value is somewhat high. In addition, the system is large and dispersion forces could be important to describe the correct activation barriers. Therefore, higher level of theory needs be used to obtain a reliable description of this system. The aim of this study is to provide a detailed theoretical analysis of this system, including all the transition states, the partition equilibria, a simple kinetic model and to use higher level of electronic structure theory in order to provide a reliable picture of this reaction system at molecular and macroscopic levels.

2. Theoretical methods

The structure of minima and transition states were full optimized using the X3LYP functional [38] with the 6-31G(d) basis set for carbon and hydrogen and the 6-31+G(d) basis set for oxygen and nitrogen. This basis set is named 6-31(+)-G(d). We should noticed that this functional is similar to the popular B3LYP one. However, the X3LYP functional is slightly more accurate than the B3LYP. The nature of stationary points were analyzed through harmonic frequency calculations and this data was used to calculate the gas phase free energy by standard statistical mechanics formulas. More extended basis set, the def2-TZVPP plus diffuse functions, has also been used [39]. In order to obtain reliable activation and interaction energies, we have make an evaluation of the

Dolling *et al.* proposed tight ion pair

Martins and Pliego most stable ion pair determined by DFT calculations



Martins and Pliego proposed transition state based on DFT calculations

Scheme 2. Proposed structures for enantioselective alkylation of indanone anion.

functionals B3LYP, X3LYP, M08-HX and M08-SO [40], using MP2 and MP4 methods in conjunction with the def2-TZVPP more diffuse basis set as benchmark.

In reported thermodynamic properties, we have used the standard state of 1 mol L⁻¹ for all species but the solvent. In the last case, we have used the pure liquid standard state and we have used the symbol ° to refer to this standard state. The solvent effect was included through the continuum SMD model [41] for toluene and the cluster-continuum model for aqueous solution [42], using the SMD model to include the continuum part. Details of this approach for chemical reactions are discussed elsewhere [43,44]. The ideal number of explicit water molecules was determined for each ionic species in aqueous solution and we have found the following clusters are the best description of the species: OH⁻(H₂O)₃, A⁻(H₂O), Na⁺(H₂O)₄. All the calculations were done with the Firefly [45] and GAMESS [46,47] programs.

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