Water influences the enantioselectivity in the proline or prolinamide-catalyzed aldol addition of acetone to isatins

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ABSTRACT

The addition of small quantities of water to the proline or prolinamide-catalyzed aldol addition of acetone to isatin can result in increased enantioselectivity. DFT B3LYP calculations with a water molecule explicitly incorporated in the aldol transition states reproduce the observed enantioselectivity.

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Organocatalysis has developed into a major field in organic synthesis, as the use of organocatalysts is environmentally beneficial and avoids the use of polluting metals. Therefore, many studies have been undertaken to develop new highly selective organocatalytic reactions.[1] Within this interesting research area, the aminocatalytic approach offers a simple and mild entry to modified aldol addition reactions. Following this approach, we have recently reported the highly enantioselective cross-aldol addition of acetone to isatins, a class of activated ketones. The reaction was carried out in commercial acetone, and several catalysts were tested. D-Pro-L-β^3-hPhg-OBn afforded the best results, with ees reaching 68% at the most.[2] The same approach succeeded in the first asymmetric total synthesis of convolutamydine A,[3,4] a member of a group of oxindole natural products with interesting biological activity.[5]

While we were investigating our reaction conditions, we realized that some water was crucial, as in the absence of water the reaction took place usually with very low yields and enantiomeric excesses. A number of research groups have pointed out the importance of water in the reaction mixture: the reactions have been classified as 'in water', 'on water', and 'in the presence of water'. In the first case, water is the solvent, in the second case water is an immiscible solvent, and in the third case the aldol addition takes place in a solvent mixture including water.[6] Examples of highly

diastereoselective and enantioselective aldol reactions in the presence of water without using any organic solvents have been reported by Hayashi[7] and Barbas III.[8] Additionally, Hayashi[9] has reported the use of a combined proline/surfactant organocatalyst in water and the use of both dry and wet proline in the absence of an organic solvent for catalysis of cross-aldol reactions. More recently, Chimni reported that some protonated proline amides in water were effective catalysts for the aldol reaction.[10]

Given our initial observation of the requirement for water in the aldol reaction, we undertook a systematic study of the quantity of water required to obtain the best results in terms of yield and stereoselectivity. The reaction has been optimized using D-Pro-OH (catalyst **1**) or D-Pro-L-β^3-hPhg-OBn (catalyst **2**) (Fig. 1).

The reaction yields and enantiomeric excesses of the addition of acetone to isatin catalyzed by **1** or **2** in the presence of variable amounts of water are reported in Table 1. In a typical reaction, isatin (50 mg, 0.3 mmol) was added to a mixture of dry acetone (2 mL, unless otherwise stated), **1** or **2** (0.03 mmol) and water (see Table 1) at −15 °C. The reaction mixture was maintained at this temper-
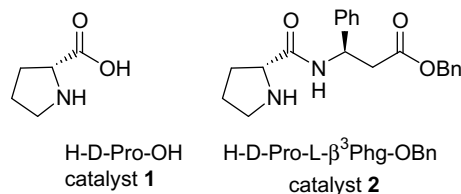
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Figure 1. Catalysts evaluated in this study.

H-D-Pro-OH
catalyst **1**

H-D-Pro-L-β^3Phg-OBn
catalyst **2**

Table 1

Enantiomeric excesses and reaction yields for the addition of acetone to isatin catalyzed by 10 mol % of D-Pro-OH (catalyst **1**) or D-Pro-L-β^3-hPhg-OBn (catalyst **2**) at −15 °C in the presence of variable amounts of water
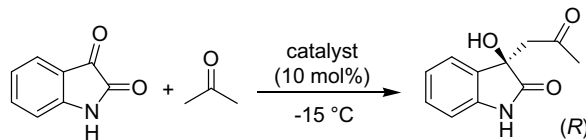
| Entry	Catalyst	Equiv H$_2$O (µL)	Equiv acetone (mL)	Time (h)	Yield (%)	ee (%)
1	**1**	0	90 (2)	90	Quant.	4
2	**1**	5 (27)	90 (2)	90	Quant.	35
3	**1**	20 (108)	90 (2)	90	31	43
4	**1**	30 (162)	90 (2)	90	40	30
5	**1**	40 (216)	90 (2)	90	14	23
6	**1**	183 (1000)	45 (1)	90	0	–
7	**1**	20[a] (243)	90 (2)	90	67	23
8	**1**	40[a] (486)	90 (2)	90	45	18
9	**2**	0	90 (2)	16	86	70
10	**2**	5 (27)	90 (2)	16	Quant.	75
11	**2**	20 (108)	90 (2)	16	Quant.	77
12	**2**	30 (162)	90 (2)	16	Quant.	76
13	**2**	40 (216)	90 (2)	16	quant.	86
14	**2**	183 (1000)	45 (1)	16	90	66
15	**2**	40[a] (486)	90 (2)	16	17	62

[a] Methanol was added instead of water.

ature for the time reported in Table 1. **1** is only very slightly soluble in the reaction mixture. In the presence of a small quantity of water (Table 1, entries 2–5), **1** is a solid or a slurry (depending on the amount of water). Whilst in the presence of more water (entry 6) only one phase is observed. D-Pro-L-β^3-hPhg-OBn, **2,** is completely soluble in the reaction mixture at any acetone/water ratio. In no instance was the formation of ice observed.

The results reported in Table 1 show an ee variation when different amounts of water are present in the reaction mixture, both with catalyst **1** (D-Pro-OH) and with catalyst **2** (D-Pro-L-β^3-hPhg-OBn), although catalyst **2** always affords better results. Furthermore, when there is too much water, the yields decrease. However, in all the experiments the (R) enantiomer was preferentially obtained. Interestingly, when water was replaced by methanol (entries 7, 8, and 15), a reduction of ee was observed. These results are in agreement with previous studies that had shown that a small amount of water can not only accelerate the reaction but also increase the enantioselectivity,[11] whereas a large excess of water can be detrimental to the reaction[12] and also show that not any protic solvent can be used in these reactions.

In order to better understand the variation of ee and yield as a function of the presence of water, the aldol addition of acetone to isatin was monitored under our best conditions (entry 13) as a function of time (Fig. 2). A small increase of the ee was observed as time evolved and the yield increased. The increase in ee as a function of time may be attributable to the formation of diastereoisomeric complexes between the catalyst and the product.[13] When a large excess of water (Table 1, entry 14) or a protic organic solvent such as methanol is included in the reaction (Table 1, entries 7, 8, and 15), then this phenomenon is suppressed. It is contrary to the strictly linear relationship between the catalyst and the ee value of the product in both inter- and intramolecular aldol transformations.[14] Non-linear asymmetric amplification in wet DMSO has been attributed to greater solubility of a single enantiomer of the amino acid in comparison with the racemic amino acid. The non-linear effects are due to the equilibrium solid–liquid phase behavior of amino acids.[15]

Theoretical calculations have been used to investigate the presence of water in the aldol reaction of acetaldehyde catalyzed by
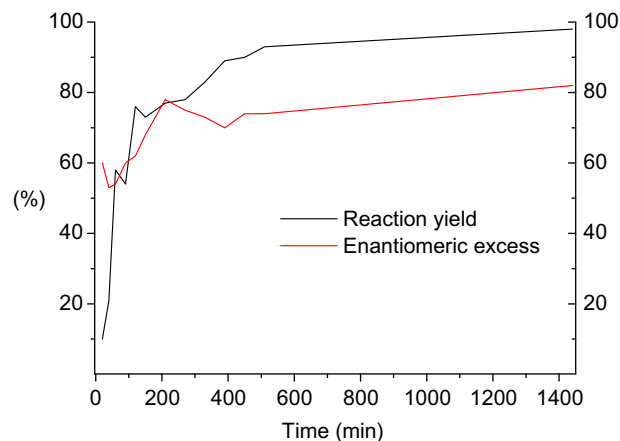
Figure 2. Enantiomeric excesses and reaction yields for the addition of acetone to isatin catalyzed by **2** (10 mol %) at −15 °C in the presence of 40 equiv of H$_2$O as a function of time.

hydroxide or by protic acid. The authors used eight water molecules and characterized the reactions as involving 3 and 2 elementary steps, respectively. The difference in the number of elementary steps was attributed to the mobility of the proton in comparison to hydroxide.[16] Water has only been incorporated in theoretical studies of the proline-catalyzed aldol addition in order to complete the reaction sequence via hydrolysis of the resultant iminium ion.[17] We are unaware of any study that has intentionally compared the results for the absence or presence of a water molecule in the proline-catalyzed aldol C–C transition states.

Given our and other groups[11] experimental results, that indicate an increase in ee of the aldol reaction in the presence of water, we questioned if the inclusion of a water molecule would have an effect upon the relative energies of the C–C aldol transition states in the case of the proline-catalyzed reaction. Our previous theoretical studies have given results that are consistent with the experimental outcome for the proline organocatalyzed reactions of isatin
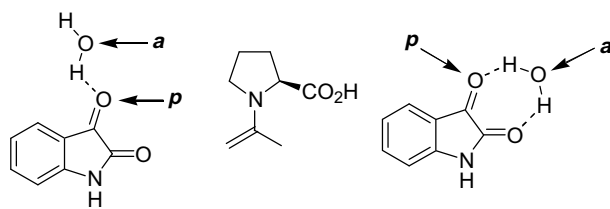
Figure 3. Water/isatin hydrogen-bonded structures. ***a*** and ***p***—respectively represent a hydrogen-bonding site for the carboxylic acid of the acetone L-proline enamine where water ***a***ctively or ***p***assively participates.

or 4-bromoisatin (as a model for 4,6-dibromoisatin) with acetone although the values for $\Delta\Delta G$ would predict much larger ee's than those observed.[18]
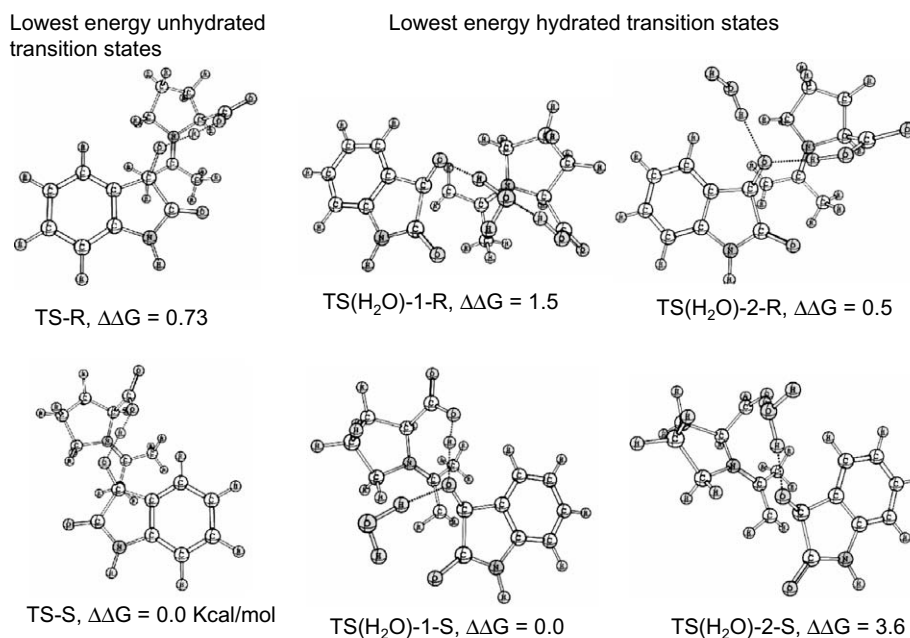
Initially, solvent compensated models were used (IEFPCM and CPCM) to study the possible effect of solvents (acetone and water) upon the relative energies of the transition states, but these methods resulted in the inversion of the relative energies for the transition states (using L-proline the R-enantiomer was favored). Therefore, in the present study we have investigated the effect of an explicitly added water molecule upon the relative energies for the diastereoisomeric aldol transition states between the acetone L-proline enamine and isatin. A single water molecule was included to form a hydrogen bond with the electrophilic carbonyl group undergoing nucleophilic addition of the enamine.[19] Two distinct situations were found, where the water molecule could actively or passively participate in the aldol TS (Fig. 3).

We used two different approaches to construct reasonable models as structural inputs for the DFT calculations.[20] The TSs from our previous study[18] were modified by the inclusion of a water molecule (passive participation of water), alternatively the water/isatin hydrogen-bonded complexes were associated with the acetone–proline enamine by the use of constraints and subsequently optimized by use of the PM3 method.[20] This method allowed investigation of both passive and active water participation in the aldol TS. The PM3-optimized structures were subsequently used as inputs for DFT B3LYP 6-31G* calculations. The two

methods overlap as they both resulted in the same transition states for passive participation of water: thus, this methodical approach gave rise to pairs of hydrated aldol transition states that we have compared with our previously calculated transition states, obtained in the absence of water (Fig. 4). Each pair of TS(H₂O) is composed of an active and a passive TS, where the water molecule hydrogen bonds to the isatin substrate in the same manner. Other higher energy-hydrated transition states were also located but have been omitted. The results reveal that the energy difference between the hydrated diastereoisomeric transition states (TS(H₂O)-1-R [or S] $\Delta\Delta G$ = 1.5 kcal/mol) is greater than that observed for the unhydrated transition states (TS-R [or S], $\Delta\Delta G$ = 0.73 kcal/mol). In the case of the pair of hydrated transition states TS(H₂O)-2-R [or S], ($\Delta\Delta G$ = 2.1 kcal/mol), the respective energies that led to formation of the R and S enantiomers result in the prediction that the R-enantiomer would be preferentially formed which is contrary to that experimentally observed for L-proline.[18]

The comparison of the two lowest energy TS structures TS(H₂O)-1-S and TS(H₂O)-2-R reveals an energy difference for $\Delta\Delta G_{298}$ = 0.5 kcal/mol. This value would very closely correspond to the enantiomeric excess (40%) experimentally observed at −15 °C.

In conclusion, we can deduce that for the experimentally studied catalysts (i) the (R) enantiomer is always favored, as we had previously demonstrated; (ii) the addition of small quantities of water (<20 equiv for D-proline catalysis) to the organocatalytic aldol reaction resulted in an increase in the enantioselectivity, whilst the addition of large quantities of water (>40 equiv for peptide catalysis) was found to be detrimental; (iii) a small increase in the ee is observed as the yield increases with time. A DFT B3LYP study involving the explicit incorporation of a water molecule in the aldol transition states resulted in two lowest energy transition states, where the water molecule passively participates, that were otherwise analogous to the lowest energy transition states in the absence of water. The calculated free energy difference ($\Delta\Delta G$) in the presence of water for these transition states closely predicted the experimentally observed enantiomeric excess when a small quantity of water is added to the aldol reactions.

Lowest energy unhydrated transition states

Lowest energy hydrated transition states

TS-R, $\Delta\Delta G$ = 0.73

TS(H₂O)-1-R, $\Delta\Delta G$ = 1.5

TS(H₂O)-2-R, $\Delta\Delta G$ = 0.5

TS-S, $\Delta\Delta G$ = 0.0 Kcal/mol

TS(H₂O)-1-S, $\Delta\Delta G$ = 0.0

TS(H₂O)-2-S, $\Delta\Delta G$ = 3.6

Figure 4. Hydrated (TS(H₂O)-1-R (or S), TS(H₂O)-2-R (or S)) and unhydrated (TS-R (or S)) transition states for the addition of the acetone L-proline enamine to isatin. All structures were calculated using B3LYP 6-31G*. Relative energies are in kcal/mol.

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