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Solvent induced enhancement of enantiomeric excess: a case study of the Henry reaction with cinchona thiourea as the catalyst†

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Enantiomeric excess (ee) in asymmetric catalysis may be strongly dependent on the solvent. The reaction product may range from an almost racemic mixture to an ee of over 90% for different solvents. We study this phenomenon for the C–C coupling reaction between nitromethane and benzaldehyde (the Henry reaction) with cinchona thiourea as the catalyst, where solvents that are strong Lewis bases induce a high ee. We show that the effect of the solvent does not consist of a change in the reaction mechanism. Instead, the solvation "prepares" the molecule, which is very flexible, in a specific conformation. The reaction barriers in this conformer are not lower than for other conformers, but are sufficiently differentiated between the enantiomers to give rise to a large ee. It is the strong Lewis basicity of the solvent that leads to the clear preference in solution for the "asymmetric" conformer. Although general rules or predictions for how solvent effects could be harnessed to produce a desired ee in general would be hard to formulate, this study does show that it is in this case (and presumably in many other cases as well) specific solute–solvent interactions rather than effects of the dielectric continuum of the solvent that are the root cause of the solvent effect. This is in agreement with experiment for the Henry reaction.

1 Introduction

The enantiomeric excess (ee) that can be achieved in asymmetric catalysis is often remarkably solvent dependent. A point in case is the Henry (or nitro-aldol) reaction with a thiourea substituted cinchona as the catalyst. The Henry reaction is a powerful synthetic tool for C–C coupling, using a nitroalkane (usually nitromethane or nitroethane) and a carbonyl compound (an aldehyde or activated ketone) as substrates.[1,2] In the case of nitromethane and benzaldehyde with cinchona thiourea as the catalyst, for instance, the reaction exhibits an ee of only 7% when carried out in neat nitromethane, but the ee increases to more than 90% with dimethylformamide (DMF) or tetrahydrofuran (THF) as the solvent.[3,4] In this paper we try to elucidate the large effect of the solvent in determining the ee.

Chiral nitroalcohols play a crucial role in enantioselective syntheses of many complex molecules.[5] They are produced *via* the Henry reaction, for which in recent years asymmetric organocatalysts[6–9] have been introduced with much success, after the original introduction of bimetallic lithium–lanthanum catalysts.[10,11] Among the organocatalysts, cinchona derivatives, Fig. 1, are extensively employed as robust stereoselective catalysts. These are flexible compounds that in solution exist as a mixture of conformers.[12,13] A good hydrogen bond donor substituent at the C$^{6'}$ position of the cinchona derivatives has proven to lead to ee.[14,15] Thiourea (Fig. 1 bottom), which is a well known organic catalyst by itself,[16,17] has been introduced as a substituent at the 6′ position, resulting in a powerful organocatalyst for the Henry reaction.[3,4]

The reaction mechanism with the cinchona thiourea catalyst has been fully elucidated using DFT calculations.[4] The calculations have confirmed that the initial step in the reaction is the abstraction of a proton from nitromethane by the basic N atom of the quinuclidine moiety. The nitromethide ion can then attack the acidic carbonyl group of the aldehyde, establishing the C–C bond. The theoretical work showed that the cinchona thiorea molecule provides a scaffold on which this reaction sequence can play out between reactants that are hydrogen bonded to the catalyst and thus brought in proximity and favorable orientation, see ref. 4 and below. Experimentally a correlation had been established between the ee and basicity of the solvent, with DMF and THF yielding the highest ee.[3,4] It was not possible to find a correlation of ee with the dielectric

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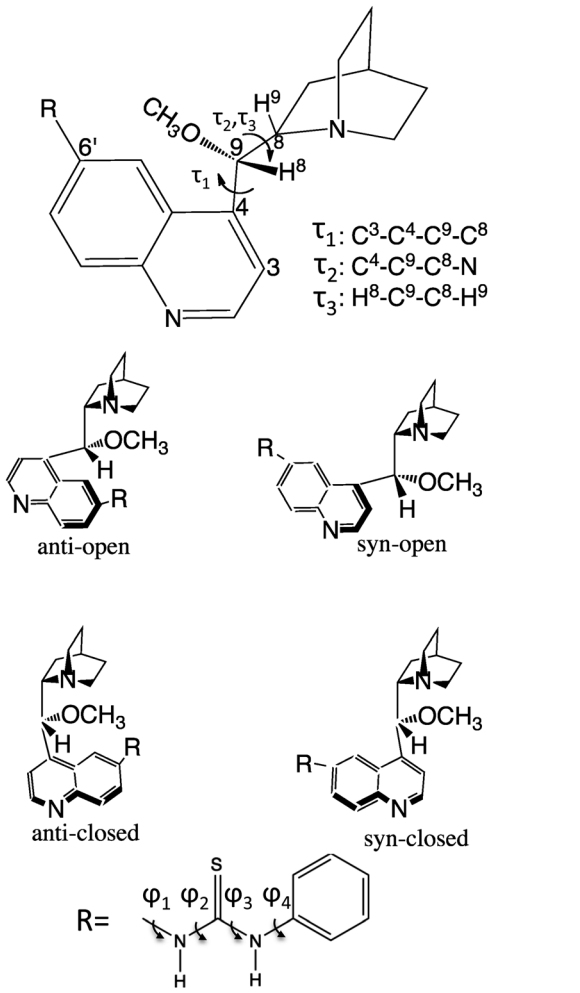

Fig. 1 The structure of cinchona alkaloid (quinidine) compounds. Upper panel: cinchona; substituting at the $C^{6\prime}$ position with hydrogen bond donors like thiourea leads to an asymmetric catalyst for the Henry reaction. τ_1, τ_2 and τ_3 angles characterize different conformers within the cinchona moiety, examples of the *anti*-open, *syn*-open, *anti*-closed and *syn*-closed conformations are shown. The φ_1, φ_2, φ_3 and φ_4 angles characterize different conformers within the thiourea moiety (bottom panel).

constant of the solvent. The theoretical work, with solvent effects only accounted for with a polarizable continuum model, gave very close transition barriers for the two enantiomers. This can be considered to be in agreement with experiment to the extent that a correlation of ee with properties of the dielectric continuum could not be established. So apparently specific interactions with solvent molecules have to be invoked, but insight into how the solvent acts to produce a high ee is still lacking and remains to be uncovered.[3,4]

We study in this work the effect of the solvent in the Henry reaction with cinchona thiourea as an effective asymmetric organocatalyst and dimethyl formamide (DMF) as the solvent. DMF has the highest Lewis basicity in the series of considered solvents in the experimental studies, and yields the highest ee.[4] We start, in Section 3, with analyzing the structure and flexibility of the catalyst in detail. Next (Section 4) the interaction between the solvent and the catalyst through formation of molecular complexes between solvent and the various cinchona thiourea conformers is studied. Also the (hydrogen bonding) interactions of the catalyst with the substrates, nitromethane and benzaldehyde, are considered. The various interaction strengths are rationalised with frontier molecular orbital considerations.

In the next step, confirming the reaction mechanism of the Henry reaction detailed in ref. 4, we investigate to what extent in this mechanism the solvent can affect the energy barriers along the reaction coordinate. The two reaction steps, proton transfer and C–C coupling are studied. It transpires that indeed the solvent plays a crucial role in steering the ee by way of "selecting", by preferential solvation stabilization, among the many possible conformers one that yields a clearly lower barrier for one of the enantiomers.

2 Computational details

Mixed torsional/low mode conformational searches were carried out by means of the Macromodel 9.7.211[18] software using Merck Molecular Force Field (MMFF) in vacuum applying a 5 kcal mol^{-1} energy window. In the conformational search, the maximum number of steps was set to 10 000.

All geometry optimizations, linear transit and frequency calculations were performed using the ADF program package.[19–21] The standard hybrid density functional B3LYP has been used (*cf.* ref. 4) and a Slater type orbital (STO) basis set of triple-zeta plus polarization functions (TZP) quality was used in all calculations, since this choice has been established as adequate.[22,23] The transition states are found using linear transit calculations in the chosen reaction coordinate, starting from converged structures and ending in an optimized stable minimum in a series of defined steps. In each linear transit calculation all degrees of freedom are fully optimized except the reaction coordinates which are constrained. The TS structures are refined with a TS search and verified to have one imaginary frequency.

3 Cinchona thiourea: molecular structure and conformers

Cinchona alkaloids (quinidine), Fig. 1, are composed of two relatively rigid entities: an aromatic quinoline ring and an aliphatic quinuclidine ring connected by an sp^3 carbon atom (chiral center C^9). The C^9 is typically hydroxylated, but to prevent an intramolecular interaction between the quinuclidine nitrogen atom and the H of the OH group at C^9, this group is usually replaced by OCH_3. The two rigid parts can rotate around the bonds connecting these moieties, see the τ_1, τ_2 and τ_3 angles defined in Fig. 1, upper panel. Depending on the different orientations of the two rigid groups, various conformers of this molecule can be obtained which are categorized into open and closed families with *anti* or *syn* orientations.[13,24–26]

In the open conformation the lone pair of the quinuclidine nitrogen points away from the quinoline ring. In the closed structure there is an interaction between the quinuclidine

nitrogen lone pair and the aromatic π orbitals. This is very important: in closed conformers the functioning of the quinuclidine nitrogen atom as a nucleophile in the catalytic pathways is hampered by the interaction inside the molecule. Rotation of the quinoline moiety around C^9–C^4, τ_1, produces *anti* and *syn* conformers. In the *anti* orientation, the R group and quinuclidine moiety are at the same side but in the *syn* orientation they are at opposite sides. The thiourea that is introduced as the R substituent,[14,16,17,27–29] brings new degrees of conformational freedom to the catalyst molecule. These are described using the φ_1, φ_2, φ_3 and φ_4 angles defined in the lower panel of Fig. 1. The possible conformations are first investigated using a molecular mechanics (MM) search in vacuum. The starting geometry for the MM search was taken from ref. 4 and depicted in Fig. 2; we call it hereafter conformer α. It can be seen in Fig. 2 that conformer α is *anti*-open for the cinchona part, while the two N–H bonds of thiourea are oriented in the same direction. The phenyl ring of the thiourea moiety is *cis* with respect to the sulfur, so it is directed away from the space between the N–H bonds and the N of the quinuclidine ring. The MM search resulted in 30 different conformers characterized by local minima. Next we optimized the obtained MM structures at the DFT level of theory (B3LYP functional and TZP basis set). The resulting relative bonding energies of all conformers in kcal mol^{-1}, with respect to the lowest one, are shown in Fig. 3. For better comparison we have divided the conformers into different families, *i.e.* open and closed, *anti* (A) and *syn* (S). The *anti*-open conformation is the best topology of the catalyst molecule for the reaction mechanism since the electrophilic (N–H bonds) and nucleophilic

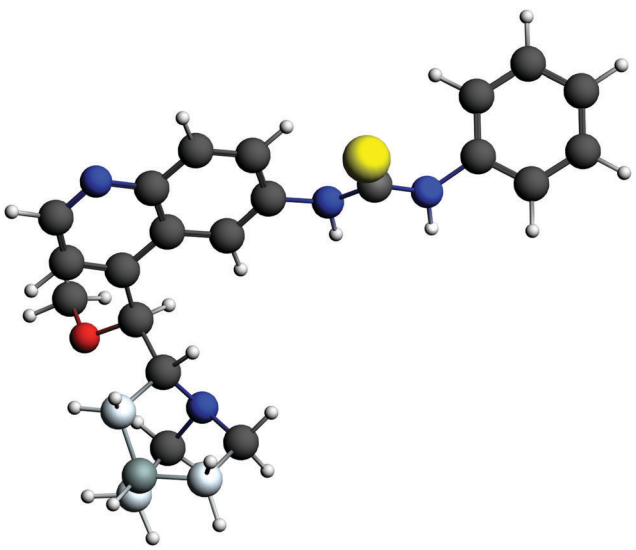

Fig. 2 The converged structure of the starting geometry for the MM search taken from ref. 4. This conformation, denoted α, has two N–H bonds of thiourea oriented in the same direction. The phenyl ring of the thiourea moiety points away from the pocket formed by quinuclidine and the two N–H groups. For a clear picture of the quinuclidine moiety, we have shown the two triads of C atoms that are connected by a threefold rotation axis with different colors, *i.e.* dark and light grey. The threefold rotation axis passes through the nitrogen and its facing carbon atom of the quinuclidine.

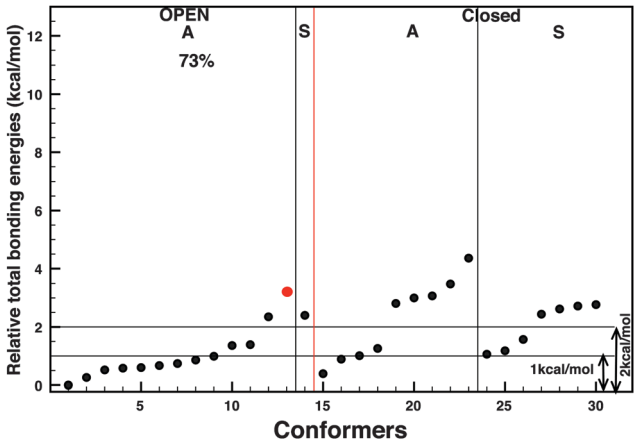

Fig. 3 Relative total energies (B3LYP/STO-TZP basis) of 30 different conformers of cinchona thiourea, grouped into families of open and closed type and of *anti* (A) and *syn* (S) types. The red symbol singles out the starting geometry of the MM search from ref. 4, which we denote as conformer α.

(nitrogen of quinuclidine) sites, which are both needed in the C–C coupling reaction mechanism (see ref. 3 and 4 and below) are in close proximity. From the Boltzmann weights, the total fraction of structures with *anti*-open conformations is 73% in vacuum at 298.15° K. As a matter of fact, practically only the conformers below 1 kcal mol^{-1} will be thermally populated, which can be seen to be in a large majority open-*anti* conformers.

We have compared the 30 geometries that resulted from the B3LYP optimization of the MM structures with optimized structures and energies of two other levels of theory, BP86/TZP and B3LYP-D/TZ2P. The picture is very similar. The starting structure of the MM conformational search, obtained from ref. 4, which we call conformer α (number **13** and which is singled out with a red symbol in Fig. 3), has with B3LYP/TZP a somewhat high relative energy of 3.2 kcal mol^{-1} compared to the lowest conformer; this is the same with BP86/TZP and B3LYP-D/TZ2P, which give 3.32 and 7.05 kcal mol^{-1} respectively. For future reference we note that α is 2.53 kcal mol^{-1} higher than conformer **6**, which will be named conformer β and will play a key role in the further discussion.

It is clear from Fig. 3 that 13 conformers have the *anti*-open conformation within the cinchona moiety. All *anti*-open conformers have similar quinoline/quinuclidine orientations. The mean values of $\tau_1 \simeq 262°$, $\tau_2 \simeq 209°$ and $\tau_3 \simeq 80°$, with a standard deviation lower than 5° over the *anti*-open conformers, have been confirmed by all three computational methods mentioned above. They only differ in the conformation of the thiourea moiety, *i.e.* in the φ_1, φ_2, φ_3 and φ_4 angles that produce different orientations of the phenyl ring, N–H and C═S groups of the thiourea moiety. As is clear in Fig. 2, in the *anti*-open conformer α, the two N–H bonds of thiourea are in the same direction and almost in the same plane but opposite to the C═S direction. However in the rest of the conformations of the *anti*-open family, other than α, the N–H bonds rather point in opposite directions (rotation over φ_3 by 180°) and the orientation of the phenyl ring also changes. These conformations are all denoted as being of type β. The distinctive feature

of these different conformations of the thiourea moiety is that in conformation α (Fig. 2) the two N–H bonds can simultaneously make hydrogen bonds with one (substrate or solvent) molecule (bi-dentate fashion), while in conformation β each N–H bond can make a hydrogen bond with a separate molecule. Rotation of the phenyl ring of thiourea towards the quinuclidine moiety in the β conformer causes steric congestion in the space between thiourea and quinuclidine moieties which may play a role in the enantioselectivity.

We will see in the next section how complexation with solvent molecules affects the conformational preferences.

4 Solvent complexation and conformational preferences

Molecular complexes of DMF solvent molecules with all 30 different conformers of the catalyst (hydrogen bonded with the N–H sites) have been formed and optimized separately. The energies of these complexes are displayed in Fig. 4.

The lower panel shows the relative energies of the molecular complexes between each conformer of the catalyst and one or two solvent molecules. The complex with conformer **6** is taken as the zero of energy in the figure. Since the complexation with the solvent molecules does not lead to serious distortion of the free molecule geometries, the numbering in Fig. 3 can be retained in Fig. 4. There is now a much stronger energetic differentiation than for the isolated conformers in Fig. 3: the number of conformers within 1 kcal mol^{-1} reduces to four, all of which are *anti*-open. The population of closed conformers decreases. The total population of *anti*-open conformers is now 91%, almost completely composed of the four low-energy conformers **2**, **4**, **6** and **7**. The solvent in a sense "selects" a few conformers, which is evidently relevant for the performance of the catalyst. It has been observed before that minimizing the number of chiral reactive species in the reaction medium to a few effective ones is crucial for obtaining a high level of steroeselectivity.[30]

The structures of two representative conformers of cinchona thiourea, with the hydrogen bonded solvent molecules, are shown in Fig. 4, upper panel. The most stable conformation, **6**, represents the β structure, which has the two N–H bonds *trans* to each other, so hydrogen bonding to two DMF molecules takes place. All four low-lying structures (**2**, **4**, **6** and **7**) are of β type. To the right in the upper panel we show the structure of the α type conformer **13** which has hydrogen bonding *via* both parallel oriented N–H bonds with a single DMF molecule. A second DMF molecule does not bind to the α conformer, in the sense that even after many steps in the geometry optimization a converged structure has not been found. Table 1 lists the relevant complexation energies of the catalyst with the solvent (DMF) molecules, from which the relative energies of the resulting species follow. Also complexation energies with the substrates nitromethane (NM) and aldehyde (ALD) are given. In order to understand the differences between the various complexation energies we refer to Fig. S1 in ESI,† with the interacting frontier orbitals (HOMO–LUMO) of all species in solution.

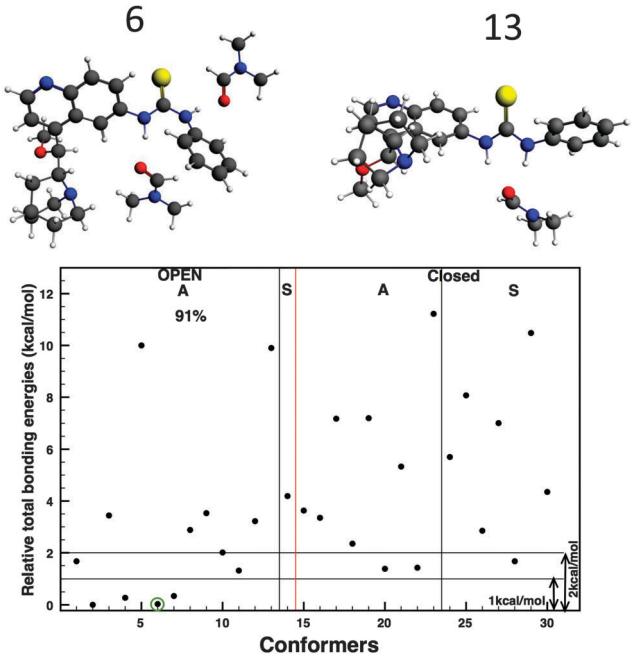

Fig. 4 Lower panel: relative total energies of 30 molecular complexes formed between the solvent (DMF) and different conformers of cinchona thiourea. Four conformational families (*anti*-open, *syn*-open, *anti*-closed and *syn*-closed) are distinguished in the figure. The numbering of the conformers is the same as Fig. 3. The lowest energy molecular complex, number **6**, is singled out with a green circle and is selected for the study of the reaction mechanism. Upper panel left: the converged structure of the lowest energy conformer, **6**, of the catalyst with two DMF solvent molecules, which is representative of the β conformers (**2**, **4**, **6** and **7** are all of β type). The two DMF molecules are hydrogen bonded to the two *trans* oriented N–H bonds. Upper panel right: the converged structure of the α type conformer **13** with the single DMF solvent molecule hydrogen bonded to both N–H bonds.

Table 1 Complexation energies (kcal mol^{-1}) with B3LYP/TZP of various substrates to the conformers α and β of cinchona thiourea. The energy zero is taken to be the free conformer β plus free substrate and solvent molecules. The energy lowering upon the various possible complexations is given (and the energy rises going from β to α). In the case of conformer β there are two different orientations of N–H bonds, denoted with superscripts 'a' (for the inward pointing N–H) and 'b' (for the outward pointing N–H). With α only one molecule can form a complex bond, as the nucleophile, to the two parallel pointing N–H bonds, and possibly to the quinuclidine N lone pair as the electrophile

Molec.	NM	ALD	DMF	DMF^b–NM^a	DMF^b–ALD^a
Free **6** = β	0.00	0.00	0.00	0.00	0.00
Complex. to a	-5.02^a	-5.45^a	-9.16^a		
Complex. to b	-6.08^b	-5.68^b	-8.67^b		
Sum of separate complex.	−11.10	−11.13	−17.83	−13.69	−14.12
Complex. to a + b simult.			−19.19	−15.16	−15.64
Free **13** = α	+2.53	+2.53	+2.53	—	—
Complex. en.	−8.51	−7.75	−11.93	—	—
Sum	−5.98	−5.22	−9.40	—	—

The highest HOMO is the non-bonding lone pair orbital of the nitrogen atom of the quinuclidine moiety. Therefore it is the strongest nucleophile in the reaction medium and is more

capable than the other nucleophiles to donate electrons to the empty C–H anti-bonding σ* orbital (LUMO + 1) of nitromethane. This σ* orbital goes down in energy rapidly when the C–H bond lengthens. Donation of the N lone pair HOMO of the catalyst molecule to the LUMO of nitromethane, which is a π* orbital localized on the NO_2 group, is not effective due to the nodal planes in this LUMO. We have explicitly checked this point by calculations, which showed that complexation between the NO_2 site of nitromethane as the electrophile and the nitrogen atom of the quinuclidine ring as the nucleophile is not possible. This also holds for the analogous carbonyl based LUMO of the aldehyde molecule. All three molecules, nitromethane, aldehyde and DMF interact as electron donors, with an oxygen based HOMO, with one (in β) or two (in α) N–H σ* acceptor orbitals of the thiourea group. The DMF, which has the highest lying HOMO, has in all cases (in α with one DMF molecule to the two N–H's and in β with a DMF molecule to $N–H^a$ and $N–H^b$ each) the strongest interaction. In Table 1 we can see that the two N–H sites of β afford two strong bonds to two DMF molecules, with a total complexation energy of almost −19.2 kcal mol^{-1} if they are present simultaneously (there is some synergy if $N–H^a$ and $N–H^b$ are hydrogen bonding simultaneously, compared to each one separately, to the amount of *ca.* −1.4 kcal mol^{-1} in the case of DMF, see Table 1). The α conformer, with only one DMF bound to it, is *ca.* 10 kcal mol^{-1} higher in energy, at −9.4 kcal mol^{-1}, indicating that in solution the β conformer is virtually the only populated one.

In order to create the reactant complex the "inner" DMF (at $N–H^a$) has to be replaced by the reactant nitromethane, which leads to a reduction of the hydrogen bonding by *ca.* 4 kcal mol^{-1} to −15.2 kcal mol^{-1}. This RC is thus easily accessible, and is considerably more favorable than the RC for the reaction with the α conformer, the α-nitromethane complex being at −6.0 kcal mol^{-1}.

Since the oxygen based HOMO of the benzaldehyde is energetically close to the HOMO of NM, the aldehyde can be a competitive candidate for hydrogen bonding with the N–H bonds. In the β conformer the bonding of the aldehyde to $N–H^a$ is actually slightly preferred over nitromethane, by *ca.* 0.4 kcal mol^{-1} whether a DMF is simultaneously complexed to $N–H^b$ or not. This small preference does not at all preclude the interchange of the aldehyde for NM. We note in passing that complexation of two of these molecules (NM or ALD) to the β conformer proves to be remarkably difficult. In particular in the case of nitromethane, it is found to be very difficult to converge a structure with two complex bound molecules. The second hydrogen bond length stays at 2.7 Å, instead of the 1.8–1.9 Å values found for the two DMF molecules. The second nitromethane appears to seek more interaction with the first nitromethane than with the $N–H^b$.

The difference of the DMF solvent with non-polar solvents, where the distribution of conformers is similar to that of free molecules in vacuum (Fig. 3), should now be clear: in non-polar solvents a large number of conformers of the catalyst exist in solution which will reduce the efficiency of the asymmetric catalyst to select one enantiomer (unless all conformations would exhibit reaction preference for the same enantiomer, which will not often be the case). However, in DMF we have a clear preference for the β conformer in solution. We will investigate in the next section if the β conformer leads to preference for one enantiomer as the reaction product.

5 Reaction barriers for the two enantiomers

A schematic representation of the Henry reaction is shown in Fig. 5. Nitromethane is converted into the nitromethide anion by abstraction of a proton. The nitromethide anion can then perform the C–C coupling by nucleophilic attack at the acidic carbonyl group of the aldehyde. The presence of the asymmetric catalyst and the solvent determines which enantiomer of the product, a secondary nitroalcohol, will be produced. With the solvents DMF and THF the enantiomeric excess (ee) can increase up to 90% and more.[3,4] A solvent effect as observed here is by no means unique.[29,31,32] We discuss in the following sections the proton transfer and the C–C coupling steps, respectively.

5.1 Proton transfer

As found in ref. 4, the complexation of nitromethane with its NO_2 group to the two N–H bonds of the α conformer will bring a nitromethane C–H bond in proximity of the basic N of quinuclidine, *i.e.* it creates a reactant complex (RC) from where the proton transfer to N can start. The same occurs for the β conformer by complexation of nitromethane to the single $N–H^a$. The proton transfer from nitromethane to the quinuclidine nitrogen atom starts by donation out of the lone pair orbital of the N of quinuclidine to the σ* orbital of the (elongating) C–H bond of the nitromethane, as can be seen in Fig. 6, upper panel, in the reactant complex (RC). In the RC the N···H (N from quinuclidine and H from nitromethane) distance is around 2.3 Å for both conformations of the catalyst (α and β). The C–H bond in the RC has lengthened by 0.014 Å by the interaction with the N lone pair, large effects of this orbital interaction only arise when the C–H σ* has come down considerably due to C–H bond lengthening. The most important distances between atoms are depicted in Fig. 6. The proton moves from the closest C–H bond to the nitrogen atom of quinuclidine. We note that in the case of conformer β there is all the time a DMF molecule coordinated to $N–H^b$. The transition states of both catalyst conformers, Fig. 6 middle panel, have been obtained by generating a two-dimensional energy surface, one variable being the distance between the H and C atoms of the CH_3 group, and the other one the distance between the same H and the N atom of the quinuclidine moiety.

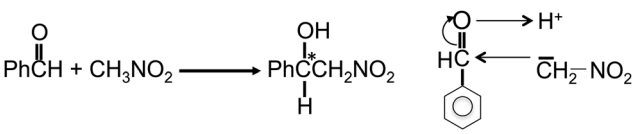

Fig. 5 Schematic representation of the Henry reaction.

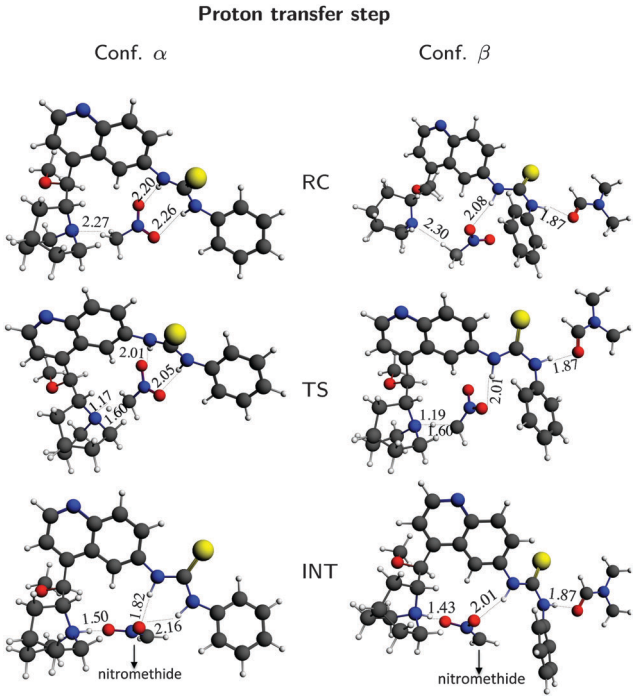

Fig. 6 Proton transfer step: optimized structures of the reactant complex (upper panel); the transition state (middle panel); and the resulting intermediate (lower panel). The most important distances between atoms are shown in the figure. Both conformers α and β are depicted.

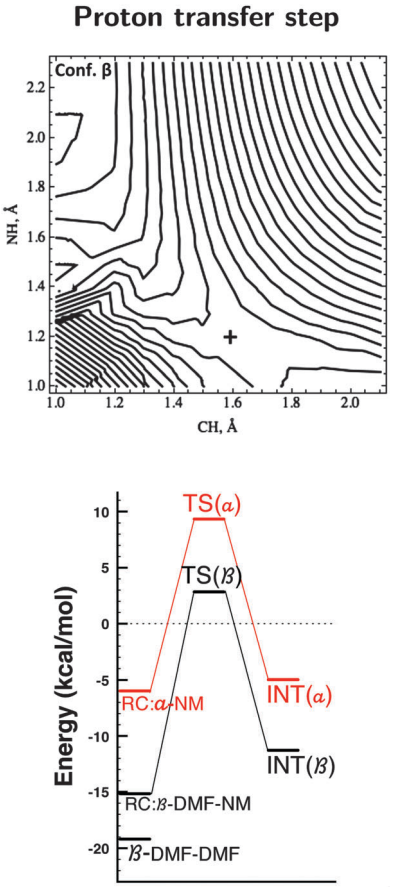

Fig. 7 Upper panel: calculated PES of the proton transfer step in the complex of β and NM. The reaction path is from the short C–H distance in the CH_3 group of NM and the long distance of H to N of quinuclidine (upper left) to long C–H and short N–H distances (lower right). The TS is indicated with a cross. Lower panel: the energy profile of the proton transfer step for both conformers α (red) and β (black). The energy zero is for the isolated species in their lowest energy conformation (cinchona thiourea-β, two DMFs, NM).

The energy surface has been obtained by mapping the N···H distance from 2.30 Å to 1.0 Å and the C···H distance from 1.1 Å to 2.1 Å using 0.1 Å steps. At each point of the surface, these two distances were constrained and all other degrees of freedom were optimized. The potential energy surface for the β conformer is shown in Fig. 7 upper panel.

The energy profile of the proton transfer step is given in Fig. 7 lower panel. The "resting state" may be considered to be the β conformer with two DMFs hydrogen bonded, at −19.2 kcal mol^{-1} below the energy zero (the collection of isolated molecules: cinchona thiourea-β, two DMFs and one nitromethane molecule) (see Table 1 for the energies). The barrier for the reaction from the RC(β) is *ca.* 18.0 kcal mol^{-1} (with respect to the free molecules it is 2.8 kcal mol^{-1}). The TS(β) is considerably below that for the α conformer, which is at +9.3 kcal mol^{-1} with respect to free molecules. If we consider the energy of the TS(α) with respect to RC(α) we obtain the energy 15.3 kcal mol^{-1}, close to the 14.7 kcal mol^{-1} reported in ref. 4 for this step. Finally the intermediate state resulting from the proton transfer (see Fig. 6, lower panel) is again considerably lower for the β conformer (at −11.3 kcal mol^{-1}) compared to the α conformer (at −5.0 kcal mol^{-1}). The lower energies that are obtained in the energy profile for the β conformer are obviously due to the additional hydrogen bonding to one DMF molecule, that can be present for the β conformer in each stage of this reaction.

5.2 C–C bond formation

The next step in the reaction is the C–C bond formation. In the intermediate, the electronic density around the carbon atom of nitromethide anion has increased and the nitromethide group has become a strong nucleophile and the perfect candidate to attack an electrophile. In the intermediate the NM molecule has turned around after the proton donation, so that the oxygen atom points to the $N–H^+$ group, and the C lone pair is available for interaction with an incoming molecule, see Fig. 6 lowest panel for the configuration in the intermediate and Fig. 8 upper panel for the incipient interaction with the aldehyde. The aldehyde molecule is an electrophile with a low lying LUMO on the carbonyl group. When the aldehyde is brought in the proximity of the negatively charged carbon atom of NM by complexation to the cinchona thiourea, the LUMO can act as the acceptor orbital for the lone pair at the C atom of nitromethide and the C–C bond is formed. In Fig. S2 in ESI† we show the frontier levels of interest: the HOMOs of the intermediates (both INT(β) and INT(α)) and the LUMO of the aldehyde. The HOMO of free nitromethane is shown for comparison. Evidently, the HOMO of the nitromethide is much higher than that of nitromethane, much closer to the LUMO of

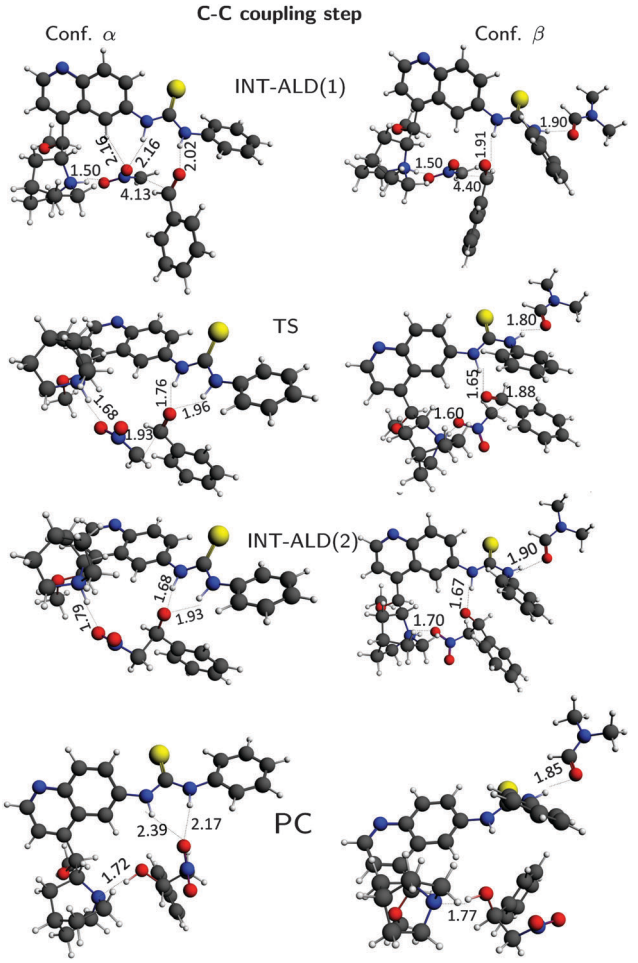

Fig. 8 Converged structures of the molecular complexes formed during the C–C bond formation step. Both conformers, α and β, of cinchona thiourea, are shown and the *S* configuration of the transition state is pictured.

the aldehyde. Also, the HOMO of INT(β) is clearly higher (by *ca.* 0.6 eV) than the one of INT(α). The Mulliken charges on the carbon atom of nitromethane/nitromethide, also shown in Fig. S2 in ESI,† are in agreement with the energy ordering: most positive on nitromethane, least positive on INT(β). We have verified that the same trend of charges is also obtained when looking at the Hirshfeld charges and/or the Voronoi deformation densities (VDD) of the corresponding carbon atom. So INT(β) is not only more stable than INT(α), it also appears to be more suited for donative interaction with the aldehyde.

The reaction is initiated with the formation of a reactant complex (RC) that is formed by complex bonding (hydrogen bonding) of the oxygen of the aldehyde with N–H of INT. In the case of INT(β) the N–H^a is the only N–H group available, so the nitromethide has to break its hydrogen bond to N–H^a (but remains bonded by the stronger oxygen with quinuclidine R_3NH^+ interaction, see Fig. 8 right upper panel). In the case of INT(α) the aldehyde can bind to N–H^b while the nitromethide remains weakly bound to N–H^a (and R_3NH^+). The complexes are rather loose, and the weak energy stabilization upon aldehyde complexation is hard to determine unambiguously. It is less than 2 kcal mol^{-1} in all cases, see Fig. 9. Fig. 8, upper panel, shows the converged structure of the molecular complex of both INT(α) and INT(β) and the aldehyde in the configuration that will yield the *S* enantiomer, denoted INT(α)-ALD (1) and INT(β)-ALD (1), respectively.

The stereo-selection is effected by the way the aldehyde molecule is coordinated to the N–H bond of the catalyst. Since benzaldehyde is a planar molecule it can be placed with either side facing the nitromethide anion. During the transition path of the C–C coupling each side will generate a different enantiomer, *S* or *R*. We have calculated both complexation modes of the benzaldehyde (only the precursor of the *S* enantiomer is shown in the figure for both α and β conformations). The reaction path is

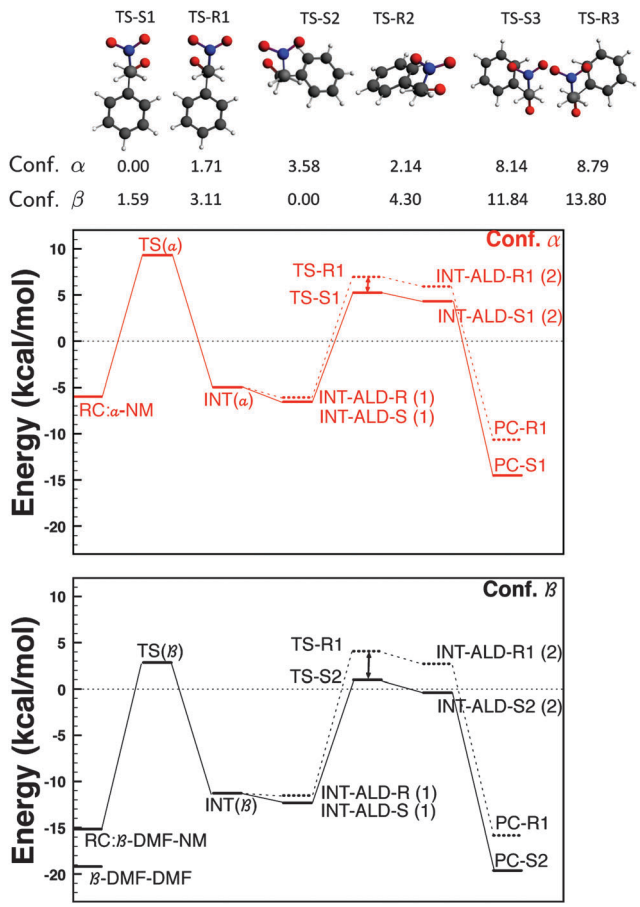

Fig. 9 The energy profile of the complete reaction path. The dashed and drawn lines are related to the C–C bond formation step of different enantiomers (*R* and *S* respectively); conformer α: upper panel; conformer β: lower panel. The relative energies are calculated with respect to the energies of the lowest conformers of the free molecules (for conformer α of the catalyst, its 2.53 kcal mol^{-1} higher energy compared to β has been considered in all complexes). The structures in the top panel show the various enantiomers. The view is down the C–C axis that is being formed, the substituents on the top C atom (which completely blocks the C atom underneath) are the phenyl group, the red oxygen and a hydrogen. The relative energies with respect to the lowest TS for each conformer (α or β) are given in kcal mol^{-1} for both conformers α and β.

then traced by gradually decreasing (in steps of 0.15 Å) the distance between the carbon atoms of the nitromethide anion and of the carbonyl group of benzaldehyde. At each point along the reaction coordinate only the C···C distance is constrained and all other degrees of freedom are fully optimized. The C–C coupling has been calculated for both conformations α and β, and in each case for both *S* and *R* enantiomers. For each enantiomer there are, also in the TS, three different conformations corresponding to the three possible Newman projections for rotation around the C···C bond that is formed between benzaldehyde and the nitromethide anion, see Fig. 8 of ref. 4 and see the top panel of Fig. 9. The nitro group of the nitromethide anion and the carbonyl oxygen of benzaldehyde are *trans* in one conformation and *gauche* in two other conformations. The *gauche* conformations (numbered 1 and 2) are much more stable than the *trans* conformations (S3 and R3 respectively). The TS-S1 is lower in energy than TS-S2 in the α conformer as was the case in ref. 4, but TS-S2 is lower in β. TS-R1 is lower than TS-R2 in both conformers (see the top panel of Fig. 9).

The energy profiles of the complete reaction path for both conformers α and β of cinchona thiourea are shown in the lower panel of Fig. 9 in red and black respectively. The drawn path shows the *S* enantiomer and the dashed one shows the *R* enantiomer.

These figures show a step in between the TS and the product complex (PC), for both *R* and *S* enantiomers in the α and β conformations of cinchona thiourea. That intermediate, called INT-ALD-*S*/*R* (2), is a C–C coupled structure in which the proton has not yet moved back from the quinuclidine R_3NH^+ group, to the O of the aldehyde to generate the final neutral nitroalcohol product. That is the last reaction step, which generates the product complexes PC-*R*/*S*. The structures of the transition state, the molecular complexes INT-ALD-S1/2 (2) and the product complexes are shown in Fig. 8. We note that only the *S* configuration has been considered in Fig. 8.

The energy barriers are given in Fig. 9 with respect to the intermediates (INT) resulting from the proton transfer step, which are stable molecular complexes (in contrast to the floppy INT-ALD-*R*/*S* (1) complexes) and can be considered for both enantiomers as good origins. As can be seen in Fig. 9, the whole energy profile for the C–C bond formation step is lower for conformer β and we first consider this conformation. Interestingly, for the conformer β the difference between the TS energies of the lowest *S* and *R* configurations, TS(β)-R1 and TS(β)-S2 is 3.1 kcal mol^{-1}. Compared to conformer α, we note that the energy barriers of the C–C formation step for the lowest *S* and *R* configurations (TS(α)-S1 and TS(α)-R1) differ by 1.7 kcal mol^{-1} for this conformer (in line with the results of ref. 4). This is only half of what has been obtained with conformer β. However, we have already concluded from the conformational and solvent complexation energetics that in a solution containing the DMF solvent and cinchona thiourea, virtually only conformation β of the catalyst will be present. For the same reason the TS(α) of the proton transfer step is so much higher in energy than the TS(β) that this reaction step will be completely dominated by the β conformer. So only the reactant complexes INT(β)-ALD-*S*/*R* (1) for the C–C coupling will be present in solution. It is therefore clear that DMF, because of being a strong Lewis base solvent, has a determining effect on the ee that is achieved. It leads to the intermediate INT(β) by the proton transfer reaction and next the INT(β)-ALD-*S*/*R* (1) as the reactant complexes from which the C–C coupling starts. The latter reaction has a sufficiently lower barrier for the formation of the *S* enantiomer to produce a large ee. It is possible to calculate the ee using the calculated Gibbs free energy difference using well established techniques.[33,34] From the full vibrational analysis for the transition states we have been able to compute the Gibbs free energies. For a better comparison of our calculated results with the experimental ones, we have re-optimized the structures of R1, R2, S1 and S2 transition states of conformer β using the catalyst molecule with two trifluoromethyl (CF_3) substituents on the phenyl ring of the thiourea moiety, catalyst **6** in ref. 4. We obtain an ee of 90% for the *S* enantiomer at 253.15° K (−20 °C). Asymmetric catalysis of the reaction by the β conformer therefore fully explains the high ee obtained experimentally in the DMF solvent.

6 Conclusions

In this study we have been able to rationalize the effect of the strong Lewis base solvent DMF on obtaining a large ee in the Henry reaction with cinchona thiourea as the catalyst. As expected, the solvent does not work in a special or spectacular way in altering the chemistry (reaction mechanism). It acts through the differentiation in the population of the conformers of the catalyst molecule by the preferential solvation of a particular conformation. The chiral nature of the catalyst molecule will naturally lead to different barriers for the production of the two enantiomers, but it is very hard to predict what the differences between the barriers will be. In the earlier study of the α conformer,[4] in which the reaction mechanism was established, the difference in barriers was too small to reach a firm conclusion on the causes for the enantiomeric preference. We have now elucidated this aspect of the reaction. The solvent effects are subtle but clear. It is just because of the sensitivity of the ee to the barrier heights, that the subtle effects of the solvation can make such an important difference for the ee. It is not possible to draw a general conclusion about solvent effects for ee from this work. It appears that the effects of solvation will be dependent on the case at hand. Maybe it is possible to predict which conformation of a chiral catalyst will be stabilized by solvation of a specific type. But then it is again hard to predict which enantiomer would benefit the most, unless there are clear steric hindrance effects. A general conclusion that emerges from our work is that the effect of DMF for the ee in the catalysis of the Henry reaction by cinchona thiourea is not specific for this molecule, but it is a property of its Lewis base character. Similar enantiomeric preference may therefore be expected from other Lewis base solvents. This is in agreement with experiment.

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