The Kinetic Stereocontrol in Brøsted Acid-catalyzed Pictet-Spengler Reaction and the Dynamic Epimerization Mechanism via Crystallization-induced Diastereomer Transformations

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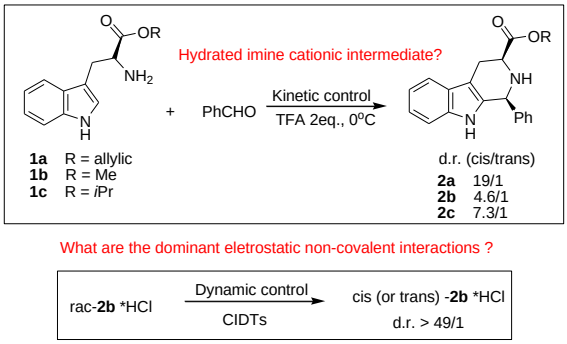
Abstract



The merging of asymmetric catalysis with crystallization-induced diastereomer transformations (CIDTs) shows promise as a practical method for the synthesis of chiral molecules with one or more epimerization carbons. A successful sample is the merging of acid-catalyzed asymmetric Pictet-Spengler reaction with CIDTs for the efficient construction of chiral complex bioactive indole alkaloids like tetrahydrocarbolines. But the rule of the kinetic control is not yet fully understood. Meanwhile the structure factor on controlling the thermodynamic diastereoselectivity (beyond the solubility factor) in epimerization of 1,3-disubstituted-tetrahydro-β-carbolines via CIDTs in organic solvent/water is also unknown. For advanced understanding of the stereocontrol, the dominant non-covalent interactions would be identified based on a hydrated imine cation model. The potential of both systems as a small molecular model for future quantitative study of biologically relevant non-covalent interactions would also be discussed.

Keywords: mechanism; non-covalent interaction; hydrated imine; on water catalysis; asymmetric catalysis; hydrogen bonding.

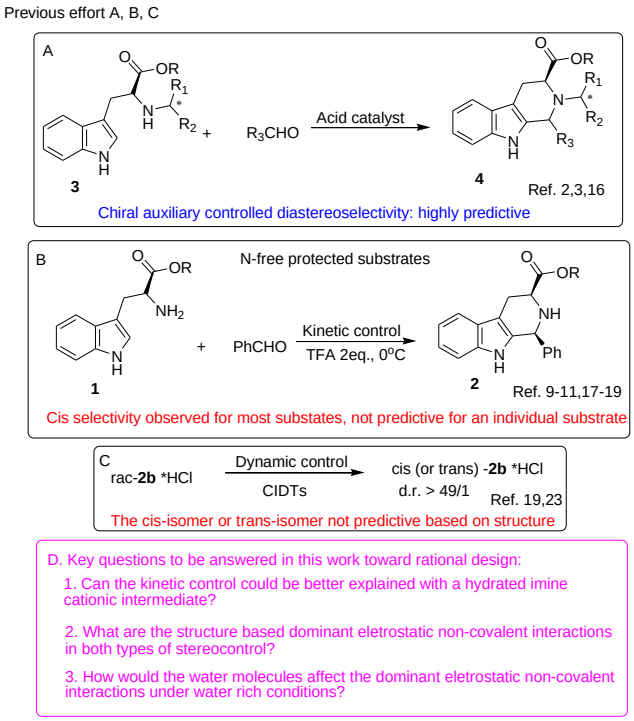
Introduction

Quantitative data[1] from reviewed literatures showed that molecules with greater stereochemical complexity tend to exhibit greater biological activity and target specificity, and over 60% of FDA-approved drugs approved between 1951 and 2021 contain one or more stereocenters. 1,3-Disubstituted-tetrahydro-β-carbolines with two stereocenters at C_1 and C_3 position could be attenable via asymmetric Pictet-Spengler reaction of readily available L/D-tryptophan derivatives with various aldehydes in the presence of acid catalysts[2-19] or enzymes (Pictet–Spenglerases)[2]. The efficient asymmetric Pictet-Spengler reaction was used as a key step for the synthesis of many drugs or bioactive complex molecules including the preparation of a commercial drug, Tadalafil[13], the preparation of HR22C16 cell permeable non-tubulin-interacting mitosis inhibitor[15], the total synthesis of a group of bioactive sarpagine-related indole alkaloids[16], the concise synthesis of natural product pyrrovobasine[17], the total synthesis of (−)-raumacline[18] , and so on. After decades' exploration, both cis-isomer and trans-isomer could be obtained by tuning the catalysts and reaction conditions from naturally abundant L-tryptophan amino acid, or its ester derivatives. Generally, strong acidic conditions favoured the formation of cis-isomer, and a majority of the reported asymmetric Pictet-Spengler reactions employed Brøsted acids as catalysts, mainly due to the fact that most of the bioactive indole alkaloids

are cis-form.[2-4] Very recently, water was reexplored as a green media via a good kinetic stereocontrol[8,12] , or via crystallization-induced diastereomer transformations (CIDTs)[19], and a good to excellent diastereoselectivity favouring cis-isomers was observed.

A two-step mechanism including an imine intermediate generation step and a subsequent Mannich condensation step was popularly proposed in most of the literatures[2-13] supported by some evidences. The auxiliary assisted asymmetric transformations by introducing a protecting group with a chiral carbon adjacent to the 1-nitrogen position proved to be effective for a predictive cis-isomer or trans-isomer based on well-established stereochemistry knowledge (Scheme 1A).[2,3,16] However, for asymmetric transformation with L/D-tryptophan derivatives free of protection of 1-nitrogen, the prediction of favouring cis-product or trans-isomer tends to be very difficult and the role of the stereocontrol is still in debate (Scheme 1B)[9-11,17-19].

Scheme 1. The previous effort and this work toward rational design



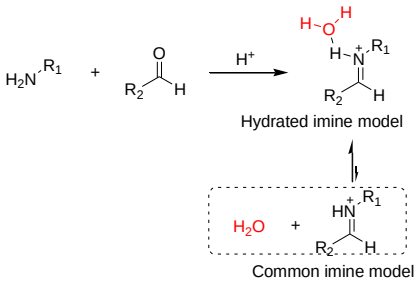
In maximizing the kinetic stereocontrol via discovering new efficient catalytic methods, it was found that some of the 1,3-disubstituted-tetrahydro-β-carbolines were not stable and the product ratios of cis-isomer/trans-isomer could possibly change via a thermodynamic racemization.[11,13,19] To utilize such thermodynamic physical properties and to avoid laborious and wasteful energy/resource-intensive purification[20-22], crystallization-induced diastereomer transformations (CIDTs)[20,21] were adopted to convert a mixture of trans/cis-1,3-disubstituted-tetrahydro-β-carboline hydrogen chlorides into a single cis-isomer or a trans-isomer in organic solvent (Scheme 1C)[23]; further expansion of the CIDTs with water as a sole solvent[19] proved to be successful and both of the isomers could be obtainable with high yield in the presence/absence of an additive in water. In a typical simple crystallization, a valuable resource of the undesirable stereoisomers would be lost, limiting the overall yield. The merged application of asymmetric Pictet-Spengler reaction and crystallization-driven selectivity could make the process quite appealing in terms of cost and efficiency because, theoretically, 100% yield is achievable via the interchanging of the other epimer. As the catalyst-mediated kinetic stereocontrol, a cis-isomer or a trans-isomer was hardly predictive; and the mechanism of the thermodynamic stereocontrol beyond the solubility factor is highly in demand for the rational design of CIDTs[19-22].

Very recently, a hydrated imine intermediate model with a water molecule close to the double bond was proposed to be dominant at the imine formation step in chiral primary amine catalysis under acidic conditions.[24] And with this model it is expected that new insights might be generated for the elucidation of the rule of kinetic stereoselective control in acid catalyzed asymmetric Pictet-Spengler reaction, along with new understandings of water ligand interactions in organic solvents (Scheme 1D)[25]. The water organic complex correlated with the ^{1}H NMR shifts of the single molecular water in the complex[25] provided a quantitative basis for the hydration capability of the common functional groups, and such hydration capability theoretically would have a strong correlation with the potential hydrogen bonding strength with acids or acidic cations. With this new knowledge, the dominant bonding interactions based on the structure of the specific 1,3-disubstituted-tetrahydro-β-carboline are proposed for explaining the dynamic stereocontrol in CIDTs in organic solvents or on water, as well as the additive reversal effect on the diastereoselectivity (Scheme 1D).

Results and discussions

Based on the knowledge that electrostatic interactions and/or electrostatics-dominated non-covalent interactions often determine the stereoselectivity in organocatalytic systems, a hydrated enamine/imine mode of two transition states (the restricted state and the relaxed state) was recently proposed to explain the diastereodivergent catalysis under both the water scarce and rich conditions.[24] A protonated imine intermediate was usually proposed in the asymmetric Pictet-Spengler reactions, and it is likely true if an imine was generated under azeotropically refluxed conditions before the addition of the acid catalyst. Under neutral or basic conditions, the bulky organic solvents would have a good advantage over imines in complexing with the single molecular water, due to the relatively low hydration capability of imines. Under acidic conditions, there is a magnitude increase of the hydration capability for protonated imines, and the imines would likely tend to keep the single molecular water stabilized by the cations (Scheme 2).[24,25] Because of the existence of the water molecule, the hydrated imine cation would have one more hydrogen atom as a donor, better participating the kinetic stereocontrol in the asymmetric Pictet-Spengler reactions.

Scheme 2. The hydrated imine model under acidic condition

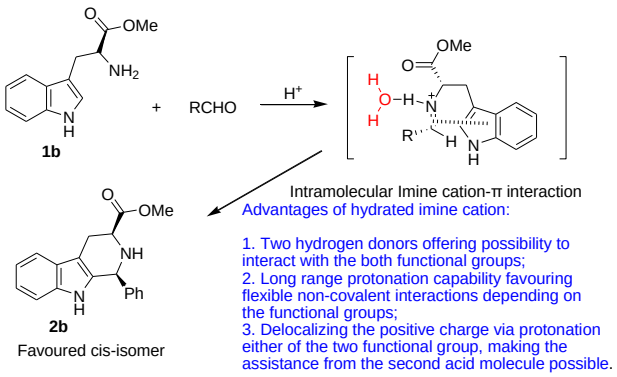


The dominant interactions in the kinetic stereocontrol

The asymmetric Pictet-Spengler reaction with L/D-tryptophan derivative (free of protection at 1-nitrogen position) as a reactant is particularly suitable for the proposed hydrated imine mode theoretically[6-9,13-15,23,27], since the protection usually increases the hydrophobicity of the imine moiety, leading to less hydration capabilities of the imine cation. Brøsted acids were used in all cases theoretically[6-9,13-15,23,27] , and excess amounts were often used. Under weak acidic conditions (for example when acetic acid was used), indole moiety was not protonated due to the weak basicity of the nitrogen atom (because the lone electron pair is involved in aromaticity).[28,29] In the presence of strong acids like trifluoroacetic acid, protonation of the indole moiety proved to be possible at C_2 or C_3 position in gas phase.[29] However, for the asymmetric Pictet-Spengler reaction with a strong acid in its

liquid phase, the protonation would likely not occur because of the already existing imine cation and a possible imine cation-π stabilization effect[30] to the indole aromatic moiety, avoiding the possible unstable dication intermediate[31]. Furthermore, even if the low concentration of the possible dication intermediate does generate, it would be highly electrophilic for the indole moiety, prohibiting the subsequent intramolecular Mannich condensation as a nucleophile.

Scheme 3. The intramolecular Cation-π interaction in kinetic stereocontrol

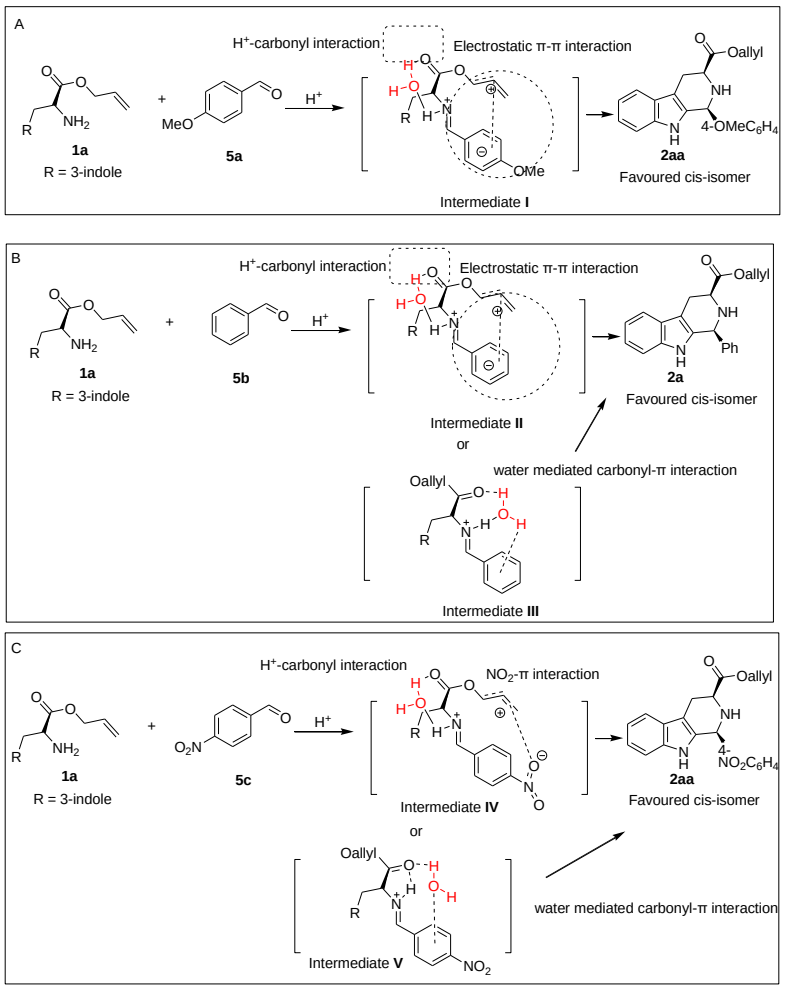


Cation-π interaction between positively charged amine and aromatic systems is increasingly recognized as an important non-covalent bonding interaction relevant to the structure biology.[30,32] The protein crystal statistics found that 26% of all tryptophans in the dataset are involved in at least one energetically significant cation-π interaction, and indole binds more tightly with the cationic amine than either benzene or phenol.[30] It is because Indole provides a much larger, more intense region of negative electrostatic potential than benzene or phenol, and it too provides a much more attractive cation-binding site.[33] Such a strong cationic imine-π interaction (indole blocking one side of the cationic imine surface) could partially explain the widely existing cis-isomeric favoured products and the non-interference of the aromatic solvents in the Brøsted acids-catalyzed asymmetric Pictet-Spengler reaction (Scheme 3)[7,9,13]. It is proposed that an intramolecular hydrate cationic imine-π interaction, rather than an intermolecular one, is preferred, although a possibility of an involved intermolecular hydrate cationic imine-π interaction cannot be ruled out. Surprisingly, there is only one report[34] that the cationic imine-π interacted intermediate was proposed to explain the stereoselectivity outcome in a chiral auxiliary mediated Pictet-Spengler reaction between a carbamate and a vinyl ether, though the cation-π interactions were already recognized as a valuable tool in controlling regioselectivity and diastereoselectivity in many organic syntheses[35].

Besides the cationic imine-π interaction, the carboxylate ester functional group from the tryptophan reactant and the functional group from aldehyde reactant were also likely involved in the kinetic control, based on the fact that both the functional groups proved to have a strong influence on the disastereoselective outcome in previous studies[6-9,13-15,23,27]. A hydrated imine model with two hydrogen donors, creating more potential and a flexibility for mediating the interaction between the functional groups, by offering a proton via a water molecule, could better explain the experimental evidences reported in the literatures. With the common imine cation model without water, the only proton on the imine nitrogen atom would likely form an energetically favoured five-membered ring intermediate the carbonyl oxygen (from the carboxylate ester functional group). The relatively rigid hydrogen bonding would offer less flexibility for the alkoxide group (from the carboxylate ester functional group), to interact with the functional group from the aldehyde reactant. In the proposed hydrated imine cationic model, the carbonyl oxygen would have the flexibility to form hydrogen bondings with the proton on the nitrogen or the hydrogen atom from the stabilized water. Such a flexibility could better explain the overall cis-selective with various aldehyde reactants, including short-chained aliphatic

aldehydes and electron-donating/withdrawn aromatic aldehydes via the H^+-π interaction[36], proton assisted carbonyl oxygen-π interaction[37] or lone pair-π interaction[36]. In the discussion below, with the hydrated cationic imine model, the dominant interactions are identified/proposed in asymmetric Pictet-Spengler reaction of L/D-tryptophan carboxylate ester, with the commonly used three reactants (benzaldehyde, 4-methoxylbenzaldehyde, 4-nitrobenzaldehyde) (Scheme 4). With each of the three substrates containing three distinct functional groups, cis-selectivity was observed for all cases[2,3,6,8,9,23]; and the mechanism behind the unusual but interesting results was not yet elucidated so far.

Scheme 4. The dominant non-covalent interactions for the asymmetric Pictet-Spengler reaction with benzaldehyde, or 4-methoxylbenzaldehyde, or 4-nitrobenzaldehyde (the hydrated imine cationic-π interaction is not displayed)



The best kinetic controlled diastereoselectivity (cis/trans > 95/5) was obtained in the presence of 2 equivalent trifluoroacetic acid at zero degrees celcius, with L-tryptophan carboxylate allylic ester and all examined aromatic aldehydes.[6] There was no obvious difference on the diastereoselectivity (cis/trans > 95/5 for all) outcome for the asymmetric Pictet-Spengler reaction with benzaldehyde, or 4-methoxylbenzaldehyde, or 4-nitrobenzaldehyde.[6] The authors found that the allylic group proved to be crucial for the excellent diastereoselectivity, upon screening the different ester functional group of L-tryptophan carboxylate ester with benzaldehyde. Only moderate diastereoselectivity was obtained (-CO_2Me, cis/trans = 4.6/1; -$CO_2{}^i$Pr, cis/trans = 7.3/1; -CO_2Bn, cis/trans = 4.7/1) when the methyl ester form/the isopropyl ester form/the benzyl ester form of L-tryptophan was employed.[9] The potential π-π interaction between the allylic group and the aromatic moiety from the aldehyde moiety was roughly

proposed in an unspecific manner by the authors in the literatures.[6,9] It is largely true for the reaction with 4-methoxylbenzaldehyde since 4-$OMeC_6H_4$ group is electronegative and the interaction with an electropositive allylic group is energetically favoured (Scheme 4A). For reactions with benzaldehyde (Scheme 4B), the phenyl group could also function as a weak electronegative aromatic to interact with the allylic group; though a competitive pathway of being protonated, and then interacting with the carbonyl group via carbonyl oxygen-π interaction[37] , may also possibly exist. However, for reactions with 4-nitrobenzaldehyde (Scheme 4C), the potential π-π stacking interaction between the highly electron-deficient aromatic moiety of 4-nitrobenzaldehyde and the same electropositive allylic group can be challenging and energetically unfavoured, due to the overall electrostatic controlled nature of the π-π interaction[38]. Instead, a carbonyl oxygen-π interaction[37] and a proton assisted NO_2-allylic (oxygen-π interaction) interaction combined (Scheme 4C) would be more favoured electrostatically and energetically. Alternatively, a lone pair-π interaction[36] between an oxygen atom in a water molecule, and nitro-substituted aromatic moiety, along with a hydrogen bonding between a water hydrogen and the carbonyl oxygen[25] are also favoured electrostatically.

For the reaction with L-tryptophan carboxylate methyl ester and benzaldehyde, the proton-assisted carbonyl oxygen-π interaction would likely be the dominant interaction. The remarkable improvement on cis selectivity (-CO_2Me, cis/trans = 4.6/1; -$CO_2{}^i$Pr, cis/trans = 7.3/1)[9] when the more electric donating isopropyl ester was used, could be explainable by improving the electrostatic interaction of the electron pair on the carbonyl oxygen in complexation with the phenyl ring[39].

It should be noted that a positive charge assistance from another molecule of trifuoroacetic acid (TFA) to the imine cationic nitrogen centre[31] may improve the kinetic control, because the protonation of aromatic moiety, nitro group or carbonyl group are expected to delocalize the positive charge on the imine cationic centre. And this is a possible reason why an excess amount of TFA was quite necessary for achieving the excellent cis selectivity. In fact, the later study[8] in aqueous media with a catalytic amount of TFA (10 mol%) showed a significant drop on the selectivity (-CO_2Me for all, benzaldehyde, cis/trans = 2.3/1; 4-methoxylbenzaldehyde, cis/trans = 1.2/1; 4-nitrobenzaldehyde, cis/trans = 3.0/1) for reactions with all three aromatic reactants. Lack of positive charge assistance from the second molecular catalyst (TFA) might be partially responsible for the loss of the selectivity, though other factors like temperature and a full hydration of reactants might also take part.

Overall, the flexible non-covalent interactions that could rearrange for more energetically favoured interactions, depending on the substrate (or functional group), are responsible for the almost exclusive cis-selectivity of the asymmetric Pictet-Spengler reaction with diversified aromatic aldehydes; and water in the hydrated imine cation may play an important role in the flexibility of the weak interactions like the water involved in the weak cooperative interactions within the biological system. Future work to confirm the dominant interactions not only would contribute to development of more efficient and predictive catalytic systems for the asymmetric Pictet-Spengler reaction, but may also offer valuable data for quantifying the biological relevant non-covalent interactions via a proper design of the experiments. It is known to be very challenging to quantify those interactions with the large biomolecules like DNA, proteins[35-39].

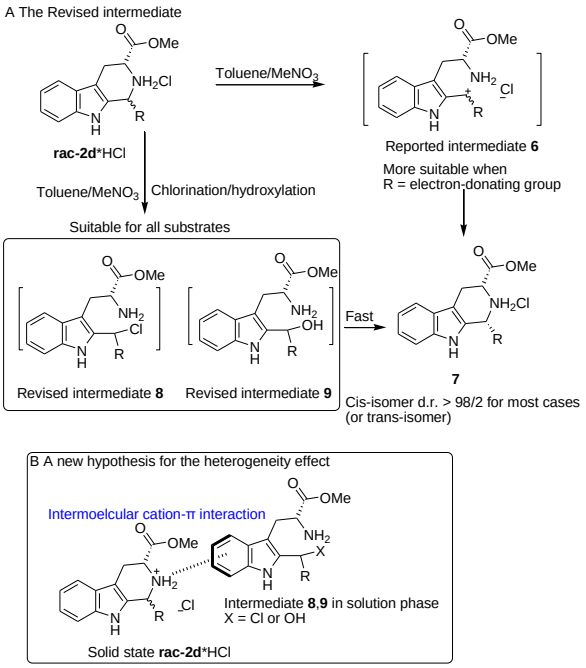
The revised mechanism and the dominant non-covalent interactions in dynamic epimerization via CIDTs in organic solvents

The successful merging of asymmetric catalysis with CIDTs offers a very practical solution for challenging substrates with one or more easy epimerization carbons. A one-pot[15] and a two-step strategy[23] have both been developed in organic solvents. A mixed solvent mixture of toluene and nitromethane proved to be the best; and outstanding diastereoselectivity (> 98/2 or > 99/1) was

observed for diversified substrates, including reactions with some aliphatic aldehydes.[23] However, to predict the cis-product outcome or the trans-product outcome was not possible simply based on the structure of a particular substrate pair under the conditions.[15,23]

Tutorially less solvated organic compounds with more intramolecular non-covalent bondings tend to crystallize out in organic solvents. An advanced understanding on the epimerization mechanism and the dominant non-covalent interactions in the solvents are expected to generate new insights toward predictable CIDTs.

Scheme 5. The revised intermediates and a new hypothesis for the heterogeneity effect

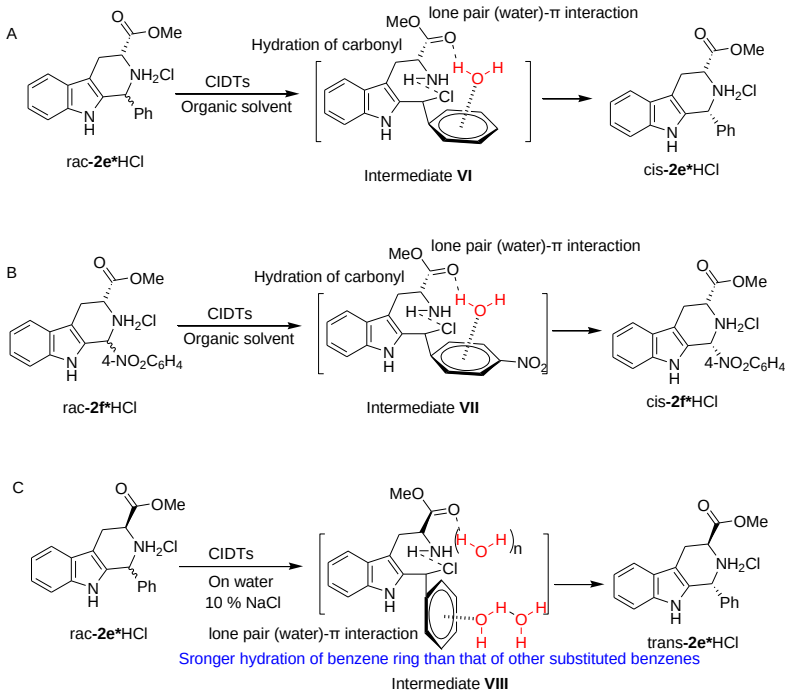


A rotatable ion pair intermediate (Scheme 5A) was proposed for the epimerization of 1,3-disubstituted-tetrahydro-β-carboline hydrogen chloride salt in toluene/nitromethane (1/1, V/V) in the literature[23] based on a deuterium labile experimental data and an intermediate trapping experimental data under reduction conditions. The proposed rotatable ion pair intermediate may be very possible for CIDTs of 1,3-disubstituted-tetrahydro-β-carboline hydrogen chloride salt with an aromatic with electron-donating functional group or aliphatic functional group at C_1-position, due to the stabilization of the carbon cation. However, for those with the strong electron-deficient aromatic functional at C_1-position, the proposed ion pair intermediate could unlikely survive electrostatically. Hence, a new intermediate with a chloride at C_1-position via C-N bond cleavage and chloride substitution is proposed here (Scheme 5A). Alternatively, a hydroxyl group replacing the chlorine atom might also be possible via water addition during the C-N bond cleavage, or a hydrolysis following the chlorination. A literature study[40,41] showed that the hydroxyl groups at the benzylic position are very reactive, and could be easily be substituted by a nucleophile inter/intramolecularly; the existence of an indole moiety at the benzylic position could likely increase the reactivity; and the reversible intramolecular amination catalyzed by HCl could be very fast toward an equilibrium in the organic solvent. It should be noted that the revised mechanism and the proposed new intermediates **8**, **9** (Scheme 5A) are still compatible with the reported experimental data[23] in the mechanistic study.

Whether the dynamic epimerization occurs via an ion pair intermediate as reported, or via a new chloride/hydroxyl intermediate, the amine moiety would lose its positive charge after the C-N bond cleavage in organic solvents. Hence the strong intramolecular cation-π interaction between the

protonated imine and indole moiety would not be possible anymore in the dynamic stereocontrol, and that is one significant difference from the dominant non-covalent interactions in the kinetic stereocontrol. Overall, the same cis-products with better diastereoselectivities were obtained in most cases.[23] The necessary heterogenous reaction conditions suggested that there might be an alternative intermolecular cation-π interaction between the protonated secondary amine (hydrogen chloride salt) in solid state, and the indole moiety of the newly proposed chloride/hydroxyl intermediate (Scheme 5B). The intermolecular cation-π interaction could better block one surface theoretically. A potential competition from another aromatic moiety (originally from aldehyde reactant) at C_1-position in intermolecular cation-π interaction, is hypothesized to favour formation of the trans-isomer via destroying the steric hinderance effect. Other non-covalent interactions like carbonyl oxygen-π interactions and lone pair-π interactions might exist in the dynamic system as well (Scheme 6A and 6B). A difference is that water hydrogen may replace the proton to mediate the two interactions, and a water molecule might stick to the carbonyl group rather than the free amine moiety due to the hydration order change.

Scheme 6. The dominant non-covalent interactions in the dynamic epimerization via CIDTs (the heterogeneous hydrated imine cationic-π interaction is not displayed)



The dominant non-covalent interactions in the dynamic epimerization via CIDTs on water

Water was found to be a very suitable solvent in the presence of 10% NaCl for the transformation of a mixture of cis and trans-1,3-disubstituted-tetrahydro-β-carboline hydrogen chloride salt into a nearly single isomer via CIDTs.[19] The epimerization reactions proceeded typically 2-4 times faster than those in toluene/nitromethane[23] for all listed substrates, particularly for aromatic substituted mixtures at C_1-position. Though the authors described the process as a "crystallization-induced asymmetric transformation in water", an "on water" mechanism[25] is here proposed to be more suitable via partial hydration, since the organic substrates are supposed to have very low solubility in water. Three major reasons might be accountable for the faster epimerization rate: 1) hydration of the secondary amine[24] promoted the chlorination/hydroxylation[26] and C-N bond cleavage; 2) the hydrophobic effect induced by water and the NaCl additive, accelerating the amination reaction after rotation; 3) partial hydration

of the aromatic moiety within the substrate forming water organic complexes[25] accelerated formation of the most stable non-covalent interactions.

The potential non-covalent interactions are suggested to be largely the same with those in CIDTs in organic solvent, based on the unchanged outstanding diastereoselectivity and the cis preference in most cases[19,23]. The experimental fact also indicated that the binding energies of the dominant non-covalent interactions like carbonyl oxygen-π interactions and lone pair-π interactions, are truly higher than that of water-water bond as calculated[36-39] limiting the insertion of water molecules. An exception was observed for the conversion of a mixture of trans/cis-1-phenyl substituted tetrahydro-β-carboline hydrogen chloride salt (Scheme 6C). The conversion via CIDTs in 10% NaCl aqueous solution produced the trans-isomer, and the reversal of diastereoselectivity on water is likely due to the relatively stronger hydration capability of benzene ring in comparison with other substituted benzenes[42].

The reversal of diastereoselectivity for CIDTs of a racemic mixture of several 1,3-disubstituted-tetrahydro-β-carboline hydrogen chloride salts on water in the presence of NaBr, NaI, or $NaNO_3$ is also observed. A mechanism of halogen anion exchanged in aqueous phase affecting the solubility ration of both isomers was proposed to be the main reason for the reversal by the authors. However, a global effect via volume increase of volume contraction of the bulky unlikely was responsible for the interesting salt effect on the diastereselectivity, based on our recent research.[43] A new hypothesis that a Na^+-assisted anion-π interaction and a subsequent stabilization by the carbonyl group might also be a possible reason theoretically, because halogen anion like Br^- or I^- was found to be able to interact with an electron-rich arene with an assistance of Na^+ in the opposite surface of the arene evidenced by the crystal data deposited at the Cambridge Structural Database[44]. If it is true for the non-covalent interaction, this protocol could be an interesting and a general method to achieve the reversal of the trans diastereoselectivity from a racemic mixture of the similar structure via CIDTs.

The dynamic epimerization via CIDTs on water shows promise as a simple small molecular model reaction for future quantitative studies of the biologically relevant non-covalent interactions like carbonyl oxygen-π interaction and lone pair (water oxygen)-π interaction, as well as anion-π interaction, towards a more specific drug design.

Conclusion

The kinetic control mechanism of diastereoselectivity in the Brøsted acid-catalyzed asymmetric Pictet-Spengler reaction between L/D-tryptophan carboxylate ester and aldehydes in organic solvents/water, was elucidated. The intramolecular cationic imine-π interaction and the substrates dependable non-covalent interactions, including the proton assisted carbonyl oxygen-π interaction and the π-π interaction, were identified as the dominant interactions for the control toward cis diastereoselectivity, based on a hydrated imine model. A revised epimerization mechanism including a chloride/hydroxyl substituted intermediate was proposed to better explain the dynamic stereocontrol. An intermolecular cationic amine-π interaction between the indole moiety in solution phase and the cationic amine in solid state was proposed to be possibly accountable for the heterogeneity advantage in achieving the prevalent cis selectivity via crystallization-induced diastereomer transformations (CIDTs) of a racemic mixture of cis and trans-1,3-disubstituted-tetrahydro-β-carboline hydrogen chloride salt in organic solvents/water. An “on water” epimerization mechanism via selective hydration of the salt form reactant was proposed to be the reason for the kinetic acceleration of CIDTs with water as a solvent. The advanced understanding is expected to inspire more future rational designs in merging the asymmetric catalysis and the CIDTs.

Both the Brøsted acid-catalyzed asymmetric Pictet-Spengler reaction and the epimerization via CIDTs in organic solvents/water show promise as a small molecular model for future quantitative investigations of the biologically relevant non-covalent interactions, towards a much more rational drug design, and an advanced understanding of the weak cooperative interactions in biological system.

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