Study of Ground State Interactions of Enantiopure Chiral Quaternary Ammonium Salts and Amides, Nitroalkanes, Nitroalkenes, Esters, Heterocycles, Ketones and Fluoroamides

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Abstract: Chiral phase-transfer catalysis provides high level of enantiocontrol, however no experimental data showed the interaction of catalysts and substrates. 1H NMR titration was carried out on Cinchona and Maruoka ammonium bromides vs. nitro, carbonyl, heterocycles, and N–F containing compounds. It was found that neural organic species and quaternary ammonium salts interacted via an ensemble of catalyst +N–C–H and (sp3)C–H, specific for each substrate studied. The correspondent BArF salts interacted with carbonys via a diverse set of +N–C–H and (sp3)C–H compared to bromides. This data suggests that BArF ammonium salts may display a different enantioselectivity profile. Although not providing quantitative data for the affinity constants, the data reported proofs that chiral ammonium salts coordinate with substrates, prior to transition state, through specific C–H positions in their structures, providing a new rational to rationalize the origin of enantioselectivity in their catalyses.

Introduction

Quaternary ammonium salts (Quats) are species widely used in synthesis and catalysis[1–4] medicinal chemistry,[5] drug discovery[6] and material science.[7] Quats have found major applications in recently developed organocatalyses where they have been used for the enantioselective formation of C–C, C–O, C–N and C–X bonds.[8,9] Enantioselective Phase-Transfer Catalysis(PTC) emerged as a notable technology within the organocatalytic domain and it has been used for the large-scale preparation of bioactive compounds[10,11] and unnatural aminoacids.[12] From an industrial standpoint, PTC offers significant advantages over other metal-free catalyses, as it is easy to scale up and the quaternary ammonium salt catalysts can be recovered by simple precipitation and filtration. Cinchona-based ammonium salts are readily available in a single step from commercial and cheap starting materials, which provides a significant advantage over other species that require longer syntheses. Since the early reports from Wynberg[13,14] and from Merck,[15,16] the area has evolved with the groups of Maruoka,[17] Jew and Park,[18] Corey[19] and Lygo[20] providing notable examples of catalyst design and relevant synthetic applications. Quats are a common motif found in a number of bioactive compounds including biocidals[21] and anticholinergics.[22] They have been intensively investigated and developed as ionic liquids[23] and – due to their similarity to acetylcholine – their supramolecular interactions with calixarenes[24] and crown ethers[25] have been also studied. The groups of Umání-Ronchi,[26] Ricci and Bernardi,[27] Jørgensen,[28] Della Sala[29] and Albanese[30] provided notable synthetic applications of...
Cinchona derived ammonium species. Adamo and coworkers have reported some highly enantioselective reactions that make use of Cinchona-based quaternary ammonium salts. Concomitantly, the groups of Waser and Vetticatt have reported the use of bifunctional quaternary ammonium salts in highly enantioselective α-fluorinations, asymmetric cascade cyclizations, Michael additions, α-hydroxylations, and α-chlorinations.

As part of these studies, we became interested in the reported mechanistic studies pertaining the key non-covalent interactions occurring between enantiopure ammonium salts and the reactants. Many groups showed that the presence of a second catalytically active functional group, i.e. an hydroxyl, had a dichotomic effect on the mechanism of catalysis, independently of the ammonium being either inherently chiral with one of the tetrahedral faces open for ion pairing or being achiral but residing in a chiral environment. Hence, chiral bifunctional ammonium salts have emerged as a powerful strategy to control the enantioselectivity in those cases where classical “monofunctional” ammoniums failed. Noteworthy, the majority of such bifunctional ammonium salts contain a free OH-group as the second coordination site. However, over the last five years, several groups have started to systematically investigate the introduction of alternative H-bonding donors, i.e. ureas and thioureas to obtain new classes of highly active bifunctional ammonium salt catalysts. Chiral back-bones were derived from the natural chiral pool like Cinchona alkaloids, amino acids, or from easily available chiral diamines, i.e. trans-cyclohexane diamine.

Hence, catalysts 1 (Figure 1), bearing an alkylated hydroxyl, can only interact with a preformed nucleophile, often an enolate, via the formation of an electrostatic interaction to form ground state preformed complex 3. The chiral environment created around the nucleophile would dictate the enantioselective bond forming reaction with an un-bound neutral electrophile (E).

On the other hand, catalyst 2 (Figure 1), bearing a free hydroxyl group, possesses two functionalities, each one able to establish a non-covalent interaction both with nucleophile (Nu) and electrophile (E) motifs. This creates the premises for two alternative pre-arrangement of Quats with their substrates. For example, the nucleophile may bind to the ammonium via an electrostatic interaction to give complex 4 (Figure 1) in which the electrophile engages with the hydroxyl via H-bonding. Alternatively, the nucleophile may establish an H-bond with the hydroxyl group forming complex 5 (Figures 1 and 2). The interaction of a neutral electrophile and a charged nucleophile in the presence of bifunctional 2, was investigated by Palomo. As part of a study reporting the addition of nitromethane to acylimines, it was unambiguously demonstrated that nitromethane enolate interacted with the hydroxyl in 2 via an H-bonding. Calculations ruled out an electrostatic interaction of nitromethane enolate with the ammonium cation, which was also a possibility. Invoked by Sanders and further computed by Houk, Palomo proposed, as a consequence, that compound 2 established an interaction with neutral electrophilic acylimines via their N–C–H protons to give complex 6 (Figure 2), in which a N–C–H–O–C H-bond was calculated possessing an energy of interaction of –6.4 kcal/mol in toluene.

In summary, the work carried out by Palomo indicated (Figure 2) two important aspects pertinent to the molecular recognition of Quats: (i) the ability of the OH to bind to an enolate via H-bonding and (ii) the crucial interaction of quaternary ammonium salts N–C–H with neutral substrates.

The data reported by Palomo were further confirmed by some observations provided by Denmark et al. indicating the involvement of at least one N–C–H in enantioselective PTC to achieve high levels of enantioselectivity. Meanwhile, strong N–C–H–O electrostatic interactions have been also invoked in other types of reactions involving Quats.

In spite of the abovementioned reports, which propose a key role of the R,N'–C–H as an H-bond donor in enantioselective catalysis, very few physical evidence have been yet
described, especially in solution, - where the catalysis takes place - and with neutral organic substrates. Donati reported the existence of intramolecular \( ^1H \) NMR spectroscopy and by X-ray crystallography.\(^{89}\) Shirakawa and others demonstrated that some quaternary ammonium salts bearing an additional electron-withdrawing group next to the ammonium accelerated the Mannich reaction via H-bonding Lewis catalysis.\(^{82-84}\) It is possible that the \( ^1N-C-H \) in Shirakawa’s catalyst was too acidic to be configurationally stable in a basic media typically required for PTC reactions and for this reason this study was limited to achiral examples. Evidence for the interaction between \( ^1N-C-H \) and alkyl chlorides was obtained via \( ^1H \) NMR titrations,\(^{82}\) which is important to determining the association of ammonium halides and their reagents. Reetz has shown by MO calculations that the charge in the case of the tetrabutylammonium unit is accessible. However, the positive nitrogen plays the role of an electron-withdrawing group for adjacent protons, rendering tetraalkylammoniums, bear a positive charge that is not directly accessible. Therefore, the presence of intramolecular electron-withdrawing group for adjacent protons, rendering them acidic enough to become good H-bond donors.\(^{86}\) Houk showed that dimethylformamide (DMF) was a particularly good ligand for ammonium species and their energy of interaction was calculated as high as \(-18.1 \text{kcal/mol}\).\(^{90}\) This calculation was in agreement with the binding energy obtained for the interaction of \((\text{CH}_3)_2\text{N}^+ \) and dimethylacetamide, which when measured by mass spectrometry ranged in the interval 18–20 kcal/mol.\(^{86}\) With this in mind, we carried out a number of \( ^1H \) NMR titrations, where \( ^1H \) NMR titrations, where \( ^1H \) NMR spectra recorded in the presence of increasing amounts of DMF as the titrant at room temperature. It should be pointed out that species 7–9 are sparingly soluble in toluene and dichloromethane and for this reason the next similar solvent, i.e. chloroform, was adopted for the NMR experiments. Although less popular than toluene or dichloromethane in phase transfer catalysis set up, due to its pronounced acidity, chloroform has been successfully used and results obtained were comparable to those of other solvents, i.e. toluene or dichloromethane.\(^{90,91}\) Hence, the conditions used in the titration experiments were similar enough to be representative of other set up carried on in different solvents. From a quantitative standpoint, it should be noted that H-bonds are stronger in less polar media; therefore, if visible in polar chloroform, the same must be formed also in less polar toluene or dichloromethane.

The chemical shifts for most representative protons of 7 are reported (Figure 3) expressed as Hz vs. the amount of DMF added (equiv.). The results collected (Figure 3) revealed that a significant shift of the \(^1H \) NMR signals for benzyllic \( H_s \), quinoline \( H_j \) and aromatic \( H_i \) could be seen (up to 40 Hz) with just 1 equiv. of titrant added. The involvement of aromatic (sp\(^3\))\(^1H \) in H-bonding has been documented\(^{92,93}\) but not on catalyst 7 and it revealed as a strong interaction. Noteworthy, it is well known that the use of the quininium vs. cinchonidinium species, or quinidinium vs. cinchoninium, in catalysis often leads to increased enantioselectivity, which based on the results provided herein, could be explained with the effect of the ortho-OCH\(_3\) to \( H_i \). Following this reasoning, the reason why ortho-OCH\(_3\) containing catalysts performed at higher enantioselectivity could be attributed to the involvement of \( H_i \) in substrate recognition and to the increased steric hindrance offered by the ortho group.

Increasing the titrant to 5 equiv. affected \( H_i \) and \( H_s \) more than the other protons in 7. It should be noted that benzyllic \( H_s \) also shifted, but to a lesser extent compared to \( H_i \). In addition, \( H_g \) shifted up-field, meanwhile \( H_s \) was progressively shifted down-field, thus confirming the directional nature of the interaction formed between DMF and 7. As should be expected, the protons around the –OH were also affected by the titration. In particular, \( H_s \), \( H_g \) and \( H_i \) shifted when larger amounts of DMF were added, identifying a secondary mode of interaction between 7 and DMF operative only at higher concentration of DMF. Hence, it was pointed out that compound 7 (Figure 3) had two sites through which an interaction with DMF occurred: a “high affinity” site (shown in light blue) defined by the benzyllic \( H_s \) and the aromatic \( H_g \), \( H_i \) and a “low affinity” site (shown in green) comprising \( H_s \), \( H_g \) and \( H_i \). In summary, compound 7

**Results and Discussion**

It has been reported that hindered organic cations, for example tetraalkylammoniums, bear a positive charge that is not directly accessible. However, the positive nitrogen plays the role of an electron-withdrawing group for adjacent protons, rendering them acidic enough to become good H-bond donors.\(^{86}\) Houk

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Figure 3. $^1$H NMR titration of N-benzyl-cinchonidinium bromide 7 with increasing aliquots of DMF. (A) shift in Hz vs. equivalents of DMF applied; (B) $^1$H NMR traces for $H_a$ and $H_b$; (C) $^1$H NMR traces for $H_c$.

Figure 4. $^1$H NMR titration of N-benzyl-cinchoninium bromide 8 with increasing aliquots of DMF. (A) shift in Hz vs. equivalents of DMF applied; (B) $^1$H NMR traces for $H_a$ and $H_c$; (C) $^1$H NMR traces for $H_b$. 
possesses two strong H-bond donors, namely (i) the benzylic $R_3N^+–CH$ and (ii) the $–OH$; apparently with $R_3N^+–CH$ being a stronger donor than $–OH$, that could be explained with the role the bromide played in the molecular interaction between 7 and DMF (see below).

The effect of different temperatures on the $^1H$ NMR titrations was also examined. Titrations were performed at 40°C and 50°C. Remarkably, $H_a$ and $H_b$ were still shifted at 40°C although to a lesser extent than at room temperature, while no shift was recorded at 50°C. These results are consistent with the disruption of H-bonding at high temperature.

We also carried out the titration of 7 and DMF in other deuterated solvents with increasing polarity: DMSO-$d_6$, MeOD, and D$_2$O. As expected, in DMSO-$d_6$, the signal shift for $H_a$ and $H_b$ was dramatically affected: the shift observed for $H_a$ was only 4 Hz (compared to 54 Hz in CDCl$_3$), while there was no appreciable shift for the other protons. In MeOD, the titration indicated no shift for the $H_a$, $H_b$, and $H_c$ signals.

This set of experiments pointed out that a stronger H-bond acceptor, capable of displacing DMF from Quats, prevented the signal shift, confirming the H-bond nature of the interaction. We then turned our attention to the pseudo-enantiomeric $N$-benzyl-cinchoninium 8 (Figure 4), which is popular for its use in many highly enantioselective reactions. We noticed that compound 8 was less soluble in CDCl$_3$ and when employed in the same amount as 7, compound 8 was only partially dissolved in the same amount of CDCl$_3$. The relative integration of a saturated solution of 8 vs. a known quantity of DMF revealed that the solution of 8 obtained was ca. 13 times more dilute compared to the one used for the titration of 7. Considering the lower concentration of 8, we were not surprised that larger amounts of DMF titrant were required to observe significant shifts.

Typically, from 10 to 50 equivalents of DMF were required to observe signal shifts comparable to those observed for 7 (Figure 4). Benzylic $H_a$ was the most shifted proton in compound 8, followed by its geminal $H_b$ and the quinoline $H_c$; as we similarly observed for compound 7. Ortho aromatic proton $H_c$ of 8 was affected to a lesser extent than 7, which we suggest is due to a different geometric arrangement of the quinoline ring relative to the quinuclidine core. The shift of geminal $H_a$ and $H_b$ also occurred in opposite directions, indicating differing anisotropy and confirming their individual engagement in H-bonding (i.e. directionality of the interaction). Proton $H_b$ was shifted also, although requiring higher concentration of titrant. This data (Figure 4) indicated once again the existence of two sites available to compound 8 through which H-bonds can form with a neutral substrate: a “high affinity” site (shown in light blue) and a “low affinity” site (shown in green). It was also confirmed that the benzylic $R_3N^+–CH$ possessed, in the presence of a coordinating anion such as bromide, higher H-bond donating ability than an $–OH$, as observed for compound 7. Having confirmed that quaternary ammonium bromides 7 and 8 established an H-bonding interaction with DMF via the benzylic...
R,N⁺–CH, we then studied the behavior of O(9)-allyl-N-benzyl-cinchonidinium bromide 9 in the same titration experiment. Compound 9 lacks a free –OH moiety, hence it has only one site available for H-bonding. Data collected (Figure 5) showed that DMF bound to 9 only via the benzylic R,N⁺–CH. Upon addition of increasing amounts of DMF to a solution of 9 in CDCl₃, protons H₁ and H₃ were the most affected alongside H₁₀ and H₁₁. These four protons identified (Figure 5) a binding site for DMF (shown in light blue). Significantly, in the ¹H NMR titration of 9 and DMF – unlike 7 with two binding modes - there was no shift observed for the H₂ and H₄ signals. This data proved that compound 9 possessed only one mode of interaction with neutral organic molecules. The demonstration that monofunctional 9 has a unique binding mode to DMF, meanwhile bifunctional 7 had two, provides an alternative explanation for the increase in enantioselectivity observed when preparing unnatural amino acids using catalysts such as 9 vs. 7.[14,15] Typically, the use of O-alkyl derivatives 9 ensured higher enantioselectivity compared to 7, which was explained by the formation of a tighter and more rigid pair formed by 9 and enolates. However, the titration experiments herein reported showed that compound 7 could interact with H-bonding acceptors, in two distinct modes. Hence, it is plausible that the increase of enantioselectivity observed by using catalysts such as 9 vs. 7 arises from the single mode of interaction available for 9 and substrates, compared to the dual modes of interaction available for 7. This data and their interpretation cast a different scenario for the mode of catalysis of compounds 7 and 9, and suggest an alternative explanation for the origin of enantioselectivity with respect to the “pyramidal” model provided by Corey.[14]

The field of enantioselective phase-transfer catalysis is dominated by two main catalyst templates, namely (i) the Cinchona-based; and (ii) Maruoka’s binaphthyl containing Quats.[5] Having established the H-bonding properties of R,N⁺–CH in the Cinchona series, we posed the question of whether the same interaction could be evidenced in Maruoka’s compounds.[5] Hence, commercially available (11bBr)-(+)–4,4-dibutyl-4,5-dihydro-2,6 bis(3,4,5-trifluorophenyl)-3H-dinaphth[2,1-c:1’,2’–e]azepinium bromide 10 was dissolved in CDCl₃ and titrated with DMF, similarly as we executed for compounds 7–9. Initial attempts failed to reveal a shift change, however, we realized that compound 10 contained two molecules of water by ¹H NMR integration (Figure 6). It was reasoned that the molecules of water may occupy the H-bond donor sites in 10, hence hampering the establishment of H-bonding between 10 and DMF. We therefore treated a solution of 10 in CDCl₃ with molecular sieves and recorded the ¹H NMR spectra at 2, 1, 0.5 and 0 equiv. of water present (Figure 6(A) and (C)). We observed that benzylic H₁ and aliphatic H₂ were subjected to a shift depending upon the equivalents of water being present in the sample. This data indicated that compound 10 must have a propensity to crystallize with two equivalents of water due to its sites available for H-bonding being operable alpha to the ammonium C–H. Aliphatic H₂ shifted of ca. 20 Hz upon dehydration. The titration experiment was then repeated on the dried solution of 10 with increasing amounts of DMF (Figure 6, (B) and (D)). The data collected indicated that benzylic H₁ and aliphatic H₂ were the most affected protons signals, hence were those interacting with DMF. Significantly, only one of the two geminal benzylic protons was shifted, once more demonstrating the directionality in the intermolecular interaction, i.e. in each CH₂ only one of the diastereotopic protons was shifted. The extent of the signal shifts for 10, though, was clearly less than those observed with the other PTCs (7–9), and required up to 100 equivalents of DMF to observe the effect.

The interaction of quaternary ammonium species possessing a β-alcohol functionality and halides has been documented.[94–96] In particular it has been reported that alcohols formed linear hydrogen bonded complexes with bromides and other halide ions in tetrachloromethane solution, which were visible at the NMR.[94] In addition, the X-ray solid state of choline chloride showed an electrostatic interaction between the proton of the OH and the halogen that kept the two species at 3.07 Å.[95] On the basis of these reports, we speculated on what role the bromide counter ion might have in the interaction of species 7–10 and DMF.

Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF) is a non-coordinating anion that has been used to identify the role of certain halogens to quaternary ammonium species.[92] It has been shown that weak H-bond acceptors such as alkyl chlorides displaced BArF from its binding to a quaternary ammonium salt. Therefore it was reasoned that DMF, a stronger acceptor, elicited the same effect.[82] In order to understand the mode of interacting of the halides in salts 7–10 and to provide further insight on their interaction with DMF, we have prepared salts 11–14 (Figures 7–10) in which the bromide was replaced by a BArF anion. Then compounds 11–14 were submitted to the same titration as 7–10. The titration of compound 11 with increasing amount of DMF showed that the OH was, alongside H₁₀, H₁, and H₂ the most affected. This result points out that the bromide must be associated with the OH primarily, then with H₁₀ in compound 7, leaving H₁ and the closely associated H₁₀ and H₂ as the main H-bond donors. Indeed, in the titration of 11, H₁ and H₂ are significantly less involved. Compound 12 (Figure 8) showed a remarkable increased solubility when compared to parent 8 and the titration was carried out at higher molar concentrations.

The results pointed out that also in this case there is a preferred interaction between DMF and H₂ alongside nearby protons H₁ and H₁₀ which was the case of compound 13 (Figure 9). The titration of compound 14 (Figure 10) showed the same behaviour of 11–13, i.e. now the H₁ shift was more pronounced compared to H₁₀ and in overall higher intensity. Once more, this data indicates that in 10 the halogen is most likely to be bound to H₁₀ which becomes the preferred H-bond donor for DMF when BArF is the counter ion. In conclusion, this dataset demonstrated that with or without an halogen counter ion, quaternary ammonium species are able to bind to the DMF through their benzylic protons, although the halogen has an impact on the mode of binding and its intensity, at least at ground state. Overall, the data herein reported suggests that BArF salts 11–14 may have completely different enantioselectiv-
ity profiles in reactions carried out with 7–10, which to the best of our knowledge is unreported.

The data collected pointed out that the N-benzyl-cinchonidinium cation, as well as the other chiral Quats herein described, interacted with DMF in two different modes, depending upon the counter ion present. This generates two diverse potential complexes, tentatively assigned as 15 and 17 (Figure 11). Quaternary ammonium species possessing a vicinal alcohol, for example choline bromide 16 (Figure 11) were shown forming linear hydrogen bonded complexes with bromides, [94,95] in which the distance between the OH and the halogen was 3.07 Å in the solid state. Therefore, the bromide in species 7–8 must be considered as “chelated” by the alcohol OH and the diffuse ammonium cation. In this context, the alcohol functionality in 7–8 was engaged with the Quats counter ion, which explains the fact that in their titration with DMF the \( ^{1}N-C-H \) hydrogen bond was invoked to explain the origin of enantioselectivity for the addition of nitromethane to acylimines. [76]

In analogy to this report, [76] and in light of the hitherto reported NMR data, we propose \( ^{1}N-C-H \) hydrogen bond to explain the origin of enantioselectivity in the addition of nitromethane 18 to 3-methyl-4-nitro-5-styrylisoxazoles 19 under the catalysis of Cinchona-based catalyst 20 (Scheme 1); [9,33] and in the enantioselective fluorination of indanone 23 performed using N-Fluorosuccinamide (NSFI) 24 under the catalysis of bifunctional ammonium thiourea 25 (Scheme 2). [45]
We have developed compounds 19 as a new class of reactive Michael acceptors that could be employed in synthesis as cinnamic ester surrogates. In compounds 19 the 4-nitroisoxazole core provides the dual function of activating the alkene towards nucleophilic addition and as a “masked carboxylate” that could be revealed via the Sarti-Fantoni

Figure 7. \(^1\)H NMR titration of N-benzyl-cinchoninium BARF-11 with increasing aliquots of DMF. (A) shift in Hz vs. equivalents of DMF applied; (B) \(^1\)H NMR traces for \(H_e\), \(H_a\), \(H_f\) and \(OH\); (C) \(^1\)H NMR traces for \(H_b\) and \(H_c\).

Figure 8. \(^1\)H NMR titration of N-benzyl-cinchoninium BARF 12 with increasing aliquots of DMF. (A) shift in Hz vs. equivalents of DMF applied; (B) \(^1\)H NMR traces for \(H_f\), \(H_a\), \(H_e\) and \(OH\); (C) \(^1\)H NMR traces for \(H_c\) and \(H_b\).
reaction, a simple procedure involving reaction of 4-nitroisoxazoles with NaOH. The reaction of 18 and 19 worked under the catalysis of cinchonidinium salt 20 providing (R)-22 in up to 97% ee. Significantly, compound 22 was obtained in only 7% ee when the O-benzyl derivative of 20 was used as the catalyst. This data indicated that a bifunctional mode of reaction was required by 20 to achieve high enantiocontrol.

As previously elaborated, Palomo has already demonstrated that in similar conditions nitromethane enolate is preferentially bond to the OH of Cinchona quaternary ammonium salts.
Although bromides, as discussed, are closely associated with the alcohol in catalysts such as 7–8, it is possible that under the reaction conditions, the halogen is exchanged for a stronger nitronate acceptor. Hence, we have postulated that in a transition state 21 (Scheme 1) leading to compound 22, the nitromethane enolate could be bound to the hydroxyl. Considering the stereochemistry generated in compound (R)-22 and the direction of attack of 18 to the pro-(R) face of 19, we considered the possibility of the nitro group of 19 being involved in H-bonding with the \(^{\text{1}}\text{N}–\text{C}–\text{H}\) of 20.\(^{[30]}\) Transition state 21, therefore, would justify the observed enantioselectivity for this and other reactions involving Michael additions to 19.\(^{[33,34]}\) In order to demonstrate this, we first carried out some calculations, by selecting tetramethylammonium as a surrogate for Quats and nitroethene as a simpler equivalent for 19. This study, executed using a B3LYP routine, which is the same algorithm as reported by Houk\(^{[78]}\) and Palomo\(^{[76]}\) for similar investigations, indicated that there were three potential H-bonding interactions (Figure 12) which could be established between the nitro oxygen atoms of 28 and \(^{\text{1}}\text{N}–\text{C}–\text{H}\) moieties present in 27. The intensity of the interaction of 27 to 28 was predicted to be \(-13.8\) kcal/mol in the gas phase, and most importantly \(-8.0\) kcal/mol in toluene (the solvent used for the enantioselective addition of nitromethane to 19).

Encouraged by these results we carried out a titration experiment using \(N\)-benzyl-cinchoninium bromide 8 with increasing aliquots of 3-methyl-4-nitro-5-styrylisoxazole 19.\(^{[30]}\) Scheme 2. Enantioselective fluorination of indanone 23.\(^{[42]}\)

![Figure 11. Tentative model of interaction between 7 and 11 with DMF, according to the \(^{\text{1}}\)H NMR titration data collected.](image1)

![Figure 12. Calculated energy of interaction between tetramethyl ammonium cation 27 and nitroethene 28.](image2)
concluded that Quats elicit strong interactions with neutral organic molecules containing polar functionalities; for example, the nitro group, via hydrogen bonding of $\text{N} - \text{C} - \text{H}$ to NO$_2$. In this regard, the similarity between the $\text{N} - \text{C} - \text{H}$ and thioureas, repeatedly reported as H-bond donors with NO$_2$ acceptors, is particularly striking.

Waser group has contributed to the field of enantioselective phase-transfer catalysis by developing a modular synthesis approach to obtain a diversified collection of catalysts 25 (Scheme 2). In all those previous reports (by others and by Waser) the beneficial effect of the H-bonding motive was clearly proven by careful control experiments. However, none of the studies performed so far have provided insight into the true activation mode of these novel catalyst motives. Based on our own interest in catalysts 25, we have thus carried out detailed transition state analyses for the $\alpha$-fluorination of $\beta$-ketoesters (Scheme 2) with the aim of: (i) getting a detailed understanding of the synergistic activation mode of the ammonium group and the H-bonding motive and (ii) using the knowledge gathered herein to develop more selective catalysts. In our initial report we postulated a very simple activation mode with the ammonium group of the catalyst ion-pairing to the enolate of the ketoester 23 and the urea coordinating the NFSI 24. However, this proposal could not be supported by any computational or additional experimental data. In order to evaluate the preferred binding mode of the bifunctional urea catalyst 25 and the two reactants 23 and 24, we carried out a detailed investigation of the C-F bond-forming step in this reaction using B3LYP/6-31G* calculations (Figure 14). A thorough conformational search was performed and transition structures leading to the major (R) and minor (S) enantiomer of 26 were located. The relative energies of the computed transition structures were evaluated by carrying out high-level single point energy calculations using B3LYP-D3(BJ)/Def2TZVPP with a PCM solvent model for m-xylene. Relative energies presented herein are the extrapolated Gibbs free energy obtained by adding the free energy correction to the high-level single point energy computed for each structure. The free energies were corrected using Grimme’s quasi rigid rotor-harmonic oscillator (qRRHO) approach, which raises vibrational frequencies that are below 100 cm$^{-1}$ to 100 cm$^{-1}$. We evaluated our originally proposed model where the enolate of 23 is stabilized by the quaternary ammonium moiety and 24 is bound to the urea moiety of the catalyst 25 (binding mode 1) and compared its relative energy to the complementary binding mode 2, where the enolate 23 is bound to the urea and 24 is bound the quaternary ammonium group of 25. Shown in Figure 14 are the lowest energy transition structures leading the major enantiomer via binding mode 1 (TS-R-BM1) and binding mode 2 (TS-R-BM2). In TS-R-BM1, the enolate of 24 is bound to the ammonium moiety via three non-conventional $\text{N} - \text{C} - \text{H}$ to O interactions (2.23 Å, 2.05 Å, and 2.44 Å) between the CH bonds $\alpha$-to the quaternary nitrogen and the two oxygen atoms of the enolate while the developing negative charge on the sulfonamide oxygen atoms of 24 is stabilized by moderately strong H-bonding interactions with the urea NHs (1.94 Å, 2.20 Å). On the other hand, TS-R-BM2 is stabilized by two strong H-bonding interactions (1.84 Å, 1.87 Å) between one of the enolate oxygen atoms and the two urea NHs and a weak...
N–C–H to O interaction with the second oxygen atom of the enolate and the cyclohexyl CH adjacent to the quaternary ammonium center. While the urea moiety binds the enolate of 23 in TS-R-BM2, the approach of 24 is directed by a weak non-conventional N–C–H to O interaction (2.59 Å) and a naphthyl (sp²)CH to O interaction (2.41 Å) to the two oxygen atoms of sulfonamide. Contrary to our original hypothesis, TS-R-BM2 was found to be 10.0 kcal/mol lower in energy than TS-R-BM1. Comparison of the key features of these transition structures suggests that this preference for binding mode 2 is likely due to the significantly stronger H-bonding interactions between the urea and the enolate of 23. Even though interactions between the CH bonds α-to the quaternary nitrogen and 24 at TS-R-BM2 might not seem significant, it is interesting to note that all transition structures where the enolate of 23 is bound to the urea moiety and 24 approaches without any interactions with the quaternary ammonium group (binding mode 3, not shown; see Supporting Information) were found to be at least 12.5 kcal/mol¹ higher in energy than TS-R-BM2. This suggests that the quaternary ammonium group has a significant role in stabilizing the transition state via both electrostatic and N–C–H to O interactions. Finally, we were able to evaluate the origin of enantioselectivity in this reaction by comparing the lowest energy transition structures leading to the R (TS-R-BM2) and S (TS-S-BM2) enantiomers of 26. While both these transition structures can be classified as proceeding via binding mode 2 (enolate of 23 bound to urea), they differ in the fact that the +F is delivered to the Re-face of the enolate in TS-R-BM2 and the Si-face of the enolate in TS-S-BM2. The slightly weaker H-bonding network of the enolate of 23 and the urea NHs in TS-S-BM2 along with possible deleterious steric interactions between the t-butyl ester of 23 and the catalyst results in TS-R-BM2 being 5.1 kcal/mol lower in energy, consistent with the high ee observed for this reaction. We recognize that this difference is quite large and a significant over-estimation of actual experimental selectivity – we attribute this to the fact that transition state optimizations were performed in the gas phase using a functional without dispersion (due to the large size of the system). Nonetheless, we believe that our thorough exploration of the phase space of this reaction has resulted in important insight into the nature of transition state stabilization orchestrated by these bifunctional quaternary ammonium-urea chiral catalysts.

Intrigued by the computational studies, indicating potential interactions between the CH bonds α-to the quaternary nitrogen and their substrates, we carried out ¹H NMR titration studies of catalyst 25 and reagents 23 and 24 (Figure 15). The ¹H NMR spectrum of catalyst 25 (Figure 15, (A)) did not show any variation upon addition of 1 equiv. of ketoester 23 and an equal amount of base (Figure 15, (B)). However, when a solution of 25 in CDCl₃ was treated with 1 equiv. of NSFI (Figure 15, (C)), two changes were immediately evident, namely: (i) the benzylic CH₂ (circled in red, Figure 15) which moved from 5.42 ppm and 5.68 ppm to coalesce at 5.40 ppm; (ii) the two ¹N(CH₃)₂ (circled in blue, Figure 11) which shifted from 2.89 ppm and 3.17 ppm to 3.05 ppm and 3.21 ppm respectively. This data showed that there was an H-bonding interaction taking place between the N–C–H of compound 8 against a range of hydrogen bond acceptors (19, 29–35, Table 1). Scope of this study was to obtain qualitative results and obtain a relative scale of preferred ligands. The results collected indicated that benzylic H₂ and H₃ and aromatic H₁ were the most affected protons. From a quantitative perspective, it was confirmed that dimethylformamide 29 was the best ligand for 8, followed by nitromethane 30 and by 3-methyl-4-nitro-5-styrylisoxazole 19. The nitro group interacted stronger with N–C–H than carbonyls of ketones and esters. Not surprisingly in view of its scarce aromaticity, 2,5-diethyl isoxazole 31 also showed significant H-bonding, although to a lesser extent.

Conclusion

In summary, we have reported physical evidence from a number of experiments, which inform on the details underpinning the interaction of popular chiral quaternary ammonium salts (Cinchona series and Maruoka-type) as H-bond donors, with a range of neutral organic H-bond acceptors such as amides, nitroalkanes, nitroalkenes, esters, heterocycles, ketones and fluoroamides. It was therefore demonstrated that amides, nitroalkanes, nitroalkenes and N-fluorobenzenesulfonimide (NSFI) are good ligands for phase-transfer catalysts with whom they establish non-classical (sp³)C–H and (sp²)C–H hydrogen bonds. We also have prepared a number of Cinchona based...
BARF salts and showed that these species are able to bind to DMF through their benzylic protons, although through the involvement of different sets of protons. Hence, the presence of an halogen has an impact on the mode of binding and its intensity, suggesting that BARF salts may have completely different enantioselectivity profiles in reactions carried out with Cinchona quaternary ammonium salts bearing an halogen as a counter-anion. The data reported mapped a set of interaction elicited by Cinchona and Maruoka-type ammonium salts when they interacted with their reactants, hence providing a model that could be used for the design of new catalyses or catalysts and to provide an explanation for the plethora of already reported high enantioselective syntheses via these species. Considering that PTC is popular in academic as well as industrial set up and that organocatalysis is nowadays considered paramount for developing green chemistry and sustainable manufacture, we believe this study will be of interest to those involved in fine chemical manufacture and enantioselective synthesis.

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Conflict of Interest
The authors declare no conflict of interest.

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The interaction between R₃NCH and NO₂ has been proposed by Shirakawa as an explanation for the recalcitrant reactivity of some nitro derivatives in Mannich reactions. See ref. [61].

Full data for the titration of N-benzyl cinchonidinium and 4-nitro-5-styrylisoxazole are reported in the Supporting Information.