# NMR Structure Determination of Ion Pairs Derived from Quinine: A Model for Templating in Asymmetric Phase-Transfer Reductions by $BH_4^-$ with Implications for Rational Design of Phase-Transfer Catalysts

Christine Hofstetter, Patricia Stone Wilkinson,† and Thomas C. Pochapsky*

*Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110*

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The solution structures of ion pairs formed by quarternary ammonium ions derived from quinine alkaloid with small hard anions ($BH_4^-$ or $Cl^-$) in $CDCl_3$ have been characterized by nuclear magnetic resonance methods. Structural observations have been correlated with the sense of asymmetric induction observed in the phase-transfer reduction of 9-anthryl trifluoromethyl ketone by borohydride ($BH_4^-$) when catalyzed by the quaternary *N*-benzylquinine ammonium ion. From interionic nuclear Overhauser effects (NOEs), it appears that the $BH_4^-$ ion occupies two of the four trigonal pyramidal sites formed by substituents of the quarternary nitrogen of the catalyst cation. One of these sites is in close proximity to the cation's hydroxyl group that is strictly required for asymmetric induction in the model reaction, while the other site is near the vinyl group on the cation. The vinyl group does not appear to be important for determining the sense or extent of asymmetric induction. Using energy-minimized structures derived from NMR data, it was predicted that the *N*-(9-methyleneanthryl)quinine−quarternary ammonium catalyst would give improved asymmetric induction in the model reaction due to a preferred anion occupancy at the site near the hydroxyl group. An improvement in enantiomeric excess (ee) is observed using the anthryl-modified catalyst, and NMR studies on the modified catalyst confirm the predicted change in anion binding site occupancies. The changes in site occupancies determined by NMR can be fitted to a simple kinetic model that correctly predicts the extent of change in ee.

## Introduction

Phase-transfer catalysis (PTC) often provides an attractive alternative for organic synthesis, as PTC reactions generally proceed under relatively mild environmentally friendly conditions.[1] PTC was initially developed to allow nucleophilic substitution upon an organic substrate using small, relatively hard anions as nucleophiles in biphasic mixtures. Typically, lipophilic cations such as quarternary ammonium or phosphonium ions have been used as catalysts in such reactions. The role of the catalyst in such reactions is primarily that of an ion shuttle. The cation forms a tight ion pair with the reagent anion, permitting the anion to be transferred into the organic phase, where it reacts with the organic substrate.

PTC has evolved considerably over the past 30 years. The role of the catalyst has also changed, especially with respect to asymmetric synthesis. In such cases, a chiral nonracemic catalyst is used to introduce asymmetry into the transition state of the reaction, thereby generating preference for one enantiomer of the product. The use of PTC for asymmetric syntheses has an added benefit in that the chiral catalysts used are generally synthesized from readily available, inexpensive starting materials derived from the chiral pool.

Although there are many papers in the literature concerning asymmetric PTC, most report low enantiomeric excesses (ee). The first report of significant ee under phase-transfer conditions was the methylation of an indanone (94%) reported in 1987 by a group at Merck.[2] Since then, several other alkylation reactions[3] and an epoxidation[4] have been achieved with high ee using chiral PTC. The common factor in these reactions is an intermediate enolate anion capable of forming an intimate ion pair with the catalyst cation. In this case, the catalyst is no longer just an ion shuttle, but acts as a template for directing the approach of the alkylating agent to one face of the prochiral enolate. In all of these reactions, the chiral phase-transfer catalysts have been quarternary ammonium salts derived from *Cinchona* alkaloids. The *Cinchona* alkaloids have been used successfully as a source of chirality in a wide variety of synthetic transformations.[5]

In 1990, we began an extensive investigation into the solution structure and dynamics of ion pairs in nonpolar solvents with an eye toward the rational design of PTCs, including chiral PTCs.[6] After noting that the phase-transfer reduction of prochiral ketones by $BH_4^-$ in the presence of catalytic quantities of the quinine-derived PTC 8α-9(*R*)-hydroxy-1-(phenylmethyl)cinchononium ("*N*-benzylquininium" or NBQ **1**, see Figure 1) chloride

* To whom correspondence should be addressed. E-mail: pochapsky@brandeis.edu. Website: http://tucano.chem.brandeis.edu.

† Current address: Bruker Instruments, Inc. Billerica, MA.

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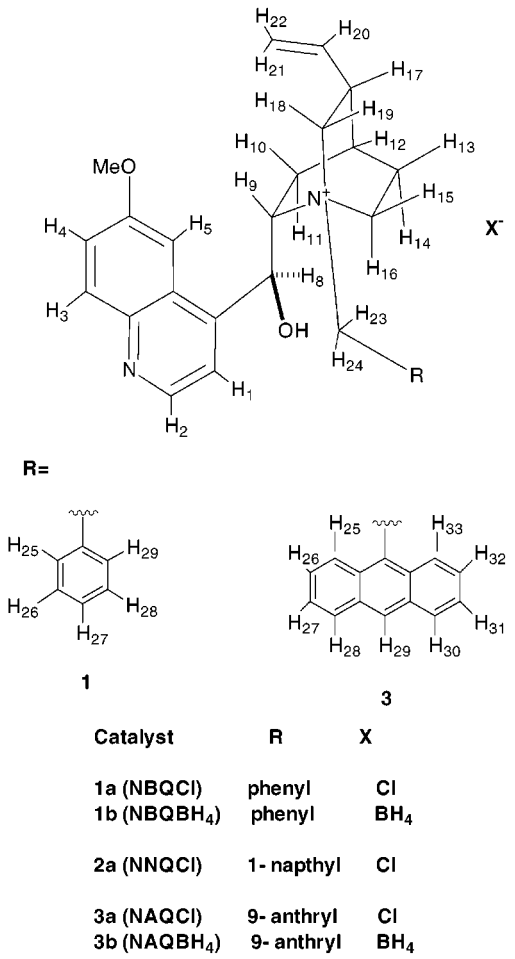
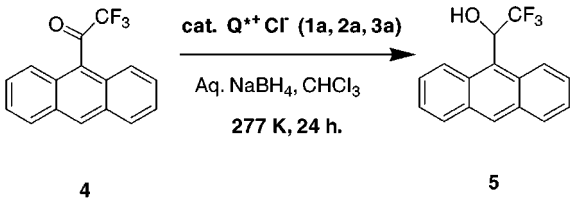



**Figure 1.** Ion pairs formed by NBQ **1**, NNQ **2**, and NAQ **3** as described previously (refs 8b and 9) and in the current work. The proton numbering scheme shown for NBQ **1** and NAQ **3** is that referred to for discussion of the NMR resonance assignments.

results in modest asymmetric induction in some cases,[7] we characterized the tight ion pair formed by NBQ and the tetrahydridoborate ($BH_4^-$) ions in order to understand the origins of asymmetry in this type of reaction.[8] We hoped that the solution structure of the ion pair might yield insights into the origin of the asymmetry induced in the products and that this information might be used to design improved chiral catalysts. On the basis of the observation of specific interionic NOEs, it was determined that the $BH_4^-$ anion binds at only two of the four trigonal pyramidal sites provided by the quaternary nitrogen of the NBQ cation in chloroform solution.[8a] One of the unoccupied sites is inside the fused quinuclidine ring system and is thus inaccessible. The other unoccupied site appears to be occluded by the benzyl group introduced upon alkylation of quinine. The two anion-occupied sites are described by their proximity to structural

**Scheme 1**

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features of the cation. One site is in the vicinity of the vinyl substituent of the quinuclidine and is called the V site, while the other is near the hydroxyl group located on the carbon α to the quinoline ring and is called the OH site.[8b,9] It has been established that the hydroxyl group near the OH site is essential for asymmetric induction in PTC-catalyzed $BH_4^-$ reductions,[10] and our hypothesis was that only anions bound at the OH site contribute significantly to the observed ee (Scheme 1). If this hypothesis is correct, then if one wished to improve the ee, it would be beneficial to block the V site, thereby increasing the relative occupancy of the OH site.[8b,9] Attempts to block the V-site exclusively (e.g., by replacing $H_{23}$ on the methylene carbon of the benzyl group with a sterically bulkier substituent, see Figure 1) have so far been unsuccessful. However, molecular modeling suggested that the V and OH anion binding sites on NBQ are not symmetric with respect to the plane of the benzyl group.[8b,9] The V-site is roughly coplanar with and adjacent to the benzyl group, while the anion in the OH site sits slightly off-plane (see Figure 2). These observations suggested to us that the replacement of the benzyl group with a larger substituent might at least partially accomplish this blocking.[8b] Although the 1-methylenenaphthyl catalyst **2a** gave only marginally better results in the PTC reduction of 9-anthryl trifluoromethyl ketone than did the benzyl catalyst (see Scheme 1 and Table 1), the 9-methyleneanthracenyl-derived catalyst **3a**, (8α-9(*R*)-hydroxy-1-(anthrylmethyl)cinchonanium chloride, or NAQCl (Figure 1)), gave significant improvement in ee (Table 1).[8b] Recently, other groups have discovered independently that the benefits of replacing the benzyl group by the 9-methyleneanthracenyl group in cinchona-derived catalysts extend to asymmetric alkylations and epoxidations as well.[3,4]

We now report the results of our examination of the solution structures of the NBQ and NAQ cations and the ion pairs they form with chloride and borohydride in nonpolar solution, to obtain insight into the origins of asymmetric induction in reductions catalyzed by these cations. The reduction used as a model reaction in the present work (Scheme 1) was chosen because of catalyst stability and ease of monitoring the results by chiral HPLC. Although no intermediate substrate anion is present to interact with the catalyst cation (hence, the modest ee relative to some asymmetric alkylations), there are also no strong bases present, so complications incurred by catalyst degradation observed in alkylation reactions[11] were not present to interfere with the NMR experiments described here.

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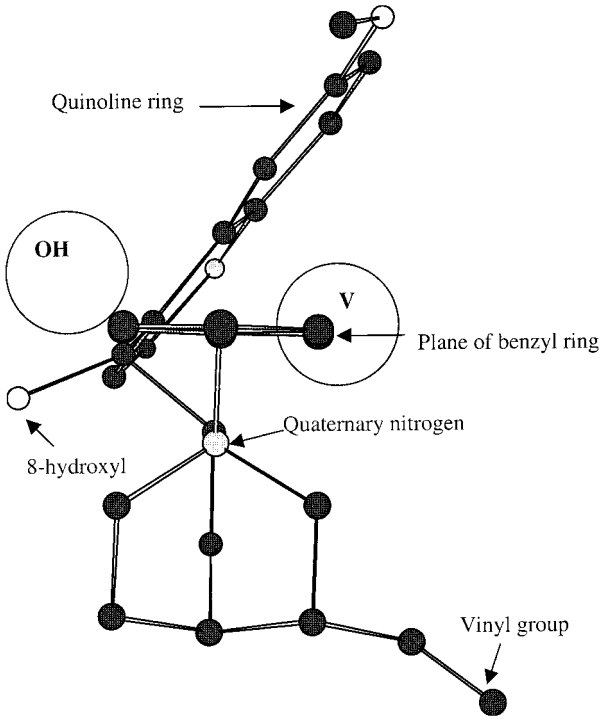


**Figure 2.** Representation of $BH_4^-$ binding sites with respect to the plane of the benzyl ring in the NBQ cation in ion pair **1b** as determined by interionic NOEs and minimization of the resulting structures. The perspective shown is down the bond between the quaternary nitrogen (shown in gray, center of the figure) and the carbon bearing $H_9$ (see Figure 1). The carbon is eclipsed by the nitrogen. The benzyl group is edge-on to the viewer. The 8-hydroxyl oxygen and the quinoline ring are both indicated by text, as is the vinyl substituent of the quinuclidine fused ring. The large circles represent the approximate positioning of the $BH_4^-$ ion in the two occupied anionic binding sites in **1b**. The circle marked OH is near the hydroxyl group, and is mostly above the plane of the benzyl ring in the perspective of the figure. The V site (closer to the vinyl group) is in the plane of benzyl ring.

**Table 1. Enantiomeric Excess (% ee) as a Function of Catalyst and Catalyst Concentration for the Reduction of Ketone 4 under Phase-Transfer Conditions (Scheme 1) (All Reactions Reported in This Table Were Performed as Described in the Experimental Section Using 0.08 M (0.5 mmol) Ketone 4 and 0.03 M (0.3 mmol) Aqueous $NaBH_4$)**

| catalyst | catalyst concn (M) | % ee (*S*)-**5** |
|---|---|---|
| **1a** | 0.008[a] | 21.4 (±0.1) |
| **1a** | 0.004 | 20.8 (±0.2) |
| **2a** | 0.008[b] | 22.8 (±0.2) |
| **3a** | 0.08 | 29.3 (±1.0) |
| **3a** | 0.04 | 30.1 (±1.2) |
| **3a** | 0.02 | 29.5 (±0.5) |
| **3a** | 0.01 | 29.5 (±0.4) |
| **3a** | 0.008[a] | 29.8 (±0.3) |
| **3a** | 0.005 | 30.1 (±0.6) |

[a] Reproduced from ref 8b. [b] Taken from ref 8b.

## Experimental Section

All reagents were used as purchased without further purification, except for $CDCl_3$, which was deacidified by passage through activated dry neutral alumina for use with $BH_4^-$-derived ion pairs.

**Preparation of 8α-9(*R*)-Hydroxy-1-(anthrylmethyl)-cinchonanium Chloride (3a).** Quinine (3 mmol, Acros) and 9-chloromethylanthracene (3 mmol, Aldrich) were added to 15 mL of benzene. The mixture was refluxed for 5 h, and the yellow solid was suction filtered after the mixture had cooled. The precipitate was then dissolved in ethanol and filtered, and the clear filtrate was evaporated under reduced pressure. The orange crystalline solid remaining was dissolved in a minimal amount of $CH_2Cl_2$. Addition of an excess of diethyl ether precipitated solid **3a** from solution. The solid was separated from solution by filtration and air-dried: mp 156−160 °C dec; $^1$H NMR assignments (italicized number corresponds to proton numbering in Figure 1, 298 K, $CDCl_3$) $\delta$ 9.27 (d, *33*), 8.7 (d, *2*), 8.51 (s, *29*), 8.40 (d, *25*), 8.06 (d, *3*), 8.04 (d, *30*), 7.99 (d, *OH*), 7.98 (d, *1*), 7.95 (d, *28*), 7.67 (m, *5 and 32*), 7.58 (m, *26*), 7.49 (m, *27 and 31*), 7.38 (dd, *4*), 7.14 (d, *23*), 7.12 (d, *8*), 6.07 (d, *24*), 5.50 (m, *20*), 5.29 (m, *16*), 4.98 (d, *22*), 4.90 (d, *21*), 4.20 (m, *9*), 3.97 (s, $OCH_3$), 3.30 (m, *18*), 2.99 (m, *15*), 2.66 (dd, *19*), 2.34 (m, *11*), 2.32 (m,*14*), 2.20 (m, *17*), 1.91 (broad, *12*), 1.51 (m, *13*), 1.48 (m, *10*); $^{13}$C NMR $\delta$ 157.9, 147.3, 144.2, 143.5, 136.5, 133.1, 132.8, 131.7 (2 C), 130.9, 130.7, 129.5, 128.6, 128.3, 127.7, 126.5, 125.4, 124.9, 124.3, 120.9 (2 C), 118.0, 117.6, 112.3, 70.1, 66.5, 60.9, 56.4, 52.1, 38.3, 25.8, 25.4, 22.5.

**Preparation of 8α-9(*R*)-Hydroxy-1-(anthrylmethyl)-cinchonanium Borohydride (3b).** A 0.2 g portion of **3a** was dissolved in 3 mL of methylene chloride, and 1.3 g of $NaBH_4$ was dissolved in 10 mL of water to which 3 drops of 3 M NaOH had been added. Half of the aqueous solution was shaken with the $CH_2Cl_2$ solution of **3a** in a separatory funnel for 2 min, and the aqueous layer was removed. The remaining aqueous solution was added to the organic layer and the procedure repeated. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure, leaving a yellowish crystalline solid: mp 144−160 °C dec; $^1$H NMR (298K, $CDCl_3$) $\delta$ 8.97 (d, 33), 8.66 (d, 2), 8.51 (s, 29), 8.19 (d, 25), 8.01 (d, 30), 7.98 (d, 3), 7.92 (d, 28), 7.85 (d, 1), 7.69 (m, 32), 7.62 (d, 5), 7.55 (m, 26), 7.51 (m, 31), 7.45 (m,27), 7.29 (dd, 4), 7.26 (d, 8), 7.05 (d, 23), 5.80 (d, 24), 5.41, (m, 20), 5.19 (m, 16), 4.99 (d, 22), 4.87 (d, 21), 4.05 (m, 9), 3.85, (s, $OCH_3$), 3.21 (m, 18), 2.73 (dd, 19), 2.34 (m, 11), 2.33 (m, 14), 1.87 (brd, 12), 1.48 (m, 13), 1.40 (m, 10); $^{13}$C NMR $\delta$ 158.0, 147.5, 144.2, 143.3, 136.5, 133.0, 132.7, 132.1, 131.9, 131.0, 130.8, 129.9, 128.6, 128.1, 126.2, 125.6, 125.0, 123.7, 120.9, 120.8, 117.7, 117.3, 101.7, 70.6, 66.2, 61.4, 56.8, 56.0, 52.5, 38.3, 25.8, 25.3, 22.0.

**Conditions for PTC Reactions.** A 0.137 g (0.5 mmol) portion of 9-anthryl trifluromethyl ketone and the desired amount of catalyst (see Table 1) was dissolved in 6.0 mL of $CHCl_3$. The aqueous layer contained 0.0114 g of $NaBH_4$ (0.3 mmol) in 10 mL of distilled water. The two solutions were combined and stirred rapidly for 24 h at 4 °C. The enantiomeric excess of the resulting 2,2,2-trifluoro-1-(9-anthryl)ethanol, **5**, was determined by chiral HPLC on a Pirkle covalent D-phenylglycine column (Regis Technologies) using 10% isopropyl alcohol in hexane as the eluent.

**NMR.** NMR experiments were performed on a Bruker AMX500 500 MHz NMR spectrometer using an inverse-detection probe equipped with three-axis gradients. Samples for NOE experiments were freeze-thaw-degassed three times. $^1$H resonance assignments are based primarily on phase-sensitive double-quantum filtered COSY and phase-sensitive two-dimensional rotating frame NOE (ROESY) spectra.[12] All NOE data described in the text were obtained from ROESY spectra. Phase sensitivity for both experiments was obtained using time-proportional phase incrementation (TPPI). DQF−COSY spectra were acquired with 4K data points in $t_2$ (direct observe) and 400 TPPI points in $t_1$. ROESY spectra were acquired with 4K data points in $t_2$ (direct observe) and 512 or 600 TPPI points in $t_1$. A compensated ROESY pulse sequence was used to correct for cross-relaxation rate dependence on frequency offset.[13] A cw spin-lock field of 2.5 kHz was applied in each experiment during a mixing time of 200 ms. Experiments were performed with different transmitter offsets in order to distinguish ROESY cross-peaks from HOHAHA-

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induced artifacts. Chemical shift assignments were measured from 1D $^1$H spectra (16K data points) when possible; otherwise, the data were obtained from the centers of COSY cross-peaks (4K data points in the directly detected dimension).

NMR diffusion measurements were made using a stimulated echo sequence incorporating pulsed field gradients.[14] A 70 ms diffusion delay was set between the two 5 ms gradient pulses, with a 5 s relaxation delay between pulse trains. Each series of eight experiments started with a gradient strength of 0.5 G/cm and increased to 16.5 G/cm. A final experiment was performed at a strength of 0.5 G/cm in order to compensate for any sample degradation during the experiment. Diffusion coefficients were calculated as described previously.[14]

1D $^{13}$C spectra were obtained on a Varian Inova 400 MHz NMR and were processed with a 5 Hz line broadening using the software on the spectrometer.

Bruker NMR data were processed on a Silicon Graphics O2 workstation using Felix97 (MSI). A 0.5−3 Hz line broadening was applied in the direct observe dimensions of all 2D experiments, and a 75−90° shifted sinebell was applied to the indirectly detected dimensions, which were then zero filled to 2K points. A zero- or first-order polynomial baseline correction was required for processing of ROESY data in the indirect detect dimension.

Diffusion experiments (16K points) were processed without window functions. Baseline (polynomial) corrections were performed as needed. Echo attenuation was measured from absolute integral values, the log of which was plotted as a function of gradient strength (see ref 14).

**Computational.** Structures of individual cations were minimized using MOPAC (PM3) or MM2 provided with Chem 3D Ultra (Cambridgesoft). Structures for the NBQ and NAQ cations were built in ChemDraw (Cambridgesoft) starting from the crystallographic structure of quinine (Cambridge Crystallographic database). Minimization calculations were performed starting with the aromatic substituent of the quaternary nitrogen coplanar with the quinoline ring, while the remainder of the structure was left unperturbed relative to the crystal structure of quinine. A grid search was used to confirm that this conformation of the aromatic substituent was in the neighborhood of the global minimum for the structure. No counterions were used in the minimizations of individual cations. Final structures were all found to be consistent with observed NOEs.

Energy minimizations of the ion pairs formed by $NBQBH_4$ **1b** used to establish the time-average positions of $BH_4^-$ in OH and V sites (Figure 2) were performed using a steepest-descents minimization routine in QUANTA/CHARMm (MSI). An NBQ cation and $BH_4^-$ anion, the structures of which had both been minimized separately, were placed relative to each other in positions determined by experimentally observed interionic NOEs. Minimization was carried out until no further relative motion was observed. No obvious conformational changes occurred in the NBQ cation as a result of the presence of the anion.

## Results

**Solution Structure of the $NBQBH_4$ Ion Pair and a Model for Asymmetric Induction in the $BH_4^-$ Reduction of 9-Anthryl Trifluoromethyl Ketone.** Our preliminary investigations of interionic NOEs in ion pair $NBQBH_4$ **1b** showed that borohydride salts of NBQ are moderately stable in $CDCl_3$, and interionic rotating frame NOEs between specific protons on the cation and the $BH_4^-$ hydride protons permit a clear identification of anionic binding sites on the chiral cation.[8a] Furthermore, the ratios of volume integrals of the NOEs associated with particular ion binding modes permit an estimate to be made of relative occupancies of the anionic binding sites. On the basis of the relative intensities of NOEs between $BH_4^-$ and protons 25, 8, 9, 16, and 18 in $NBQBH_4$ **1b** (Table 2), it was established that two sites, V and OH (vide supra), are occupied equally on a time average.[8b,9]

**Table 2. Summary of Integrated 2D NOE Volumes Measured between $BH_4^-$ Protons and Protons on the NBQ 1b and NAQ 3b Cations (Units Are Arbitrary and Comparable Only within a Column)**

| NOE from $BH_4$ to $^1$H | $NBQBH_4$ **1b** NOE volume | $NAQBH_4$ **3b** NOE volume |
|---|---|---|
| 33 (OH) | *a* | 3.2 (±0.8) |
| 25 (V) | *a* | 1.3 (±0.7) |
| 23 (OH) | 24 (±2) | 0.96 (±0.34) |
| 24 (V) | 23 (±2) | 0.47 (±0.15) |
| 16 (OH) | 33 (±5) | 0.63 (±0.13) |
| 18 (V) | 27 (±7) | 0.34 (±0.11) |
| 8 (OH) | 28 (±8) | 2.1 (±0.4) |
| 9 (V) | 30 (±11) | 0.98 (±0.22) |

*a* Overlapped signals. Volume integral is 35 (±9).

We wished to ascertain whether the observed site occupancies have any influence upon the sense and extent of asymmetric induction in phase-transfer reductions of prochiral ketones by $BH_4^-$ catalyzed by NBQCl **1a**. We proposed a model for the complex between ketone **4** and the NBQ cation **1** that rationalized the observed sense of asymmetric induction in light of what is known concerning structural requirements of the PTC (Figure 3).[8b] It has been shown that the hydroxyl group α to the quinoline ring (adjacent to the OH site) is important in the generation of asymmetry in these reductions.[10] Alkylation of the hydroxyl group greatly reduces the extent of asymmetric induction, giving nearly racemic product in Scheme 1.[15] In our model, the hydroxyl group acts as a proton donor to the carbonyl oxygen of the substrate, while stacking interactions between the quinoline ring of the catalyst and anthryl ring on the substrate orient the *Si* face close to the $BH_4^-$ for delivery of the hydride to the carbonyl carbon of the substrate, resulting in the formation of the (*S*)-enantiomer of **5** (Figure 3). Only reaction with $BH_4^-$ bound at the OH site is expected to result in significant ee in the product alcohol **5**.

If $BH_4^-$ bound to the OH site is responsible for the observed asymmetric induction, then blocking the V site (at which bound $BH_4^-$ is assumed to give rise to racemic product) might be expected to improve the observed ee by increasing the relative concentration of $BH_4^-$ in the OH site. We made several attempts to block the V site by N-alkylating quinine with α-substituted benzyl groups (i.e., 1-chloro-1-phenylethane or diphenylchloromethane), so that the proton adjacent to the V site would be replaced by a sterically larger group. To date, these attempts have been unsuccessful (vide supra). However, inspection of an energy-minimized model for the structure of the $NBQBH_4$ ion pair **1b** suggested a possible means of at least partially blocking the V site. As described above, we observed that the V and OH sites are not symmetrically disposed around the quaternary nitrogen (Figure 2). We predicted that introduction of an aryl group larger than benzyl should block the V site to a greater extent than the OH site, and lead to preferred $BH_4^-$ occupancy at the OH site. The alkylation of quinine with 1-chloromethylnaphthalene produced catalyst NNQCl **2a**; this salt gave only marginally higher ee than **1a** in

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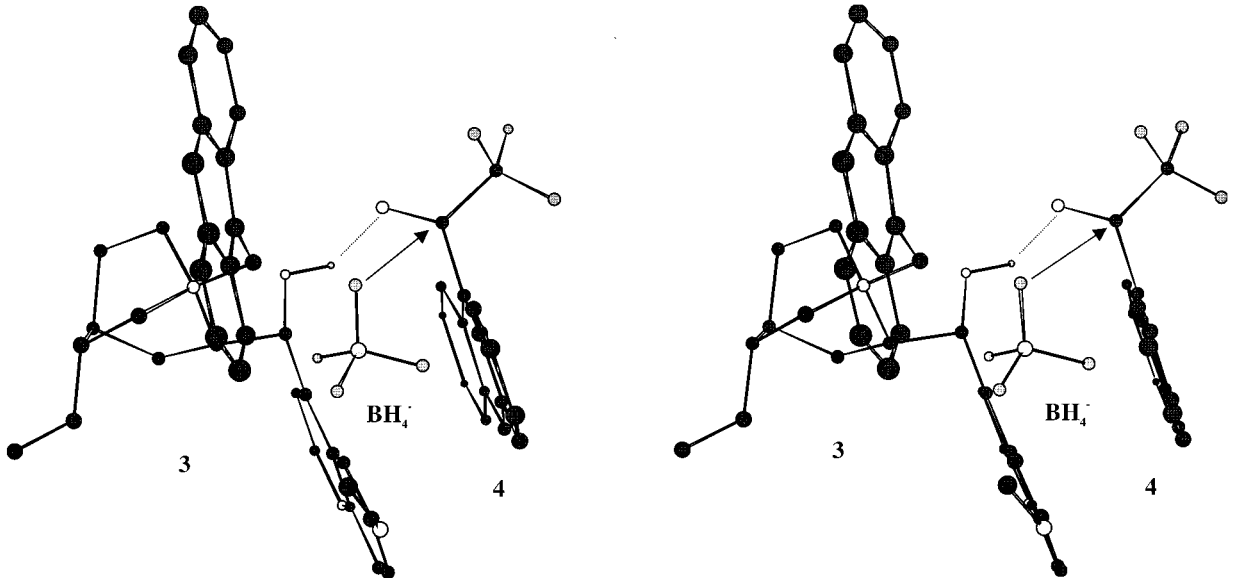



**Figure 3.** Stereoview of MM2-minimized model for the NAQ cation **3**−ketone **4** complex that rationalizes the observed enantiomeric excess for the reduction of ketone **4** under phase-transfer conditions (Scheme 1). Carbon atoms are black, oxygen atoms are white, and nitrogen, fluorine, and all $BH_4^-$ atoms are gray. Only the hydrogens of the NAQ hydroxyl and of the $BH_4^-$ anion are shown; all other hydrogens are hidden for clarity. The anthryl group of the NAQ cation **3** in the foreground and the quinoline ring in the lower background. The $BH_4^-$ is placed in the OH binding site (see Figure 2 and text). Ketone **4** (right side of figure) is arranged so as permit hydrogen bonding between the carbonyl oxygen of **4** and the NAQ **3** hydroxyl proton (indicated by a dotted line) while stacking the anthryl ring of **4** over the quinoline ring of **3**. The arrangement shown gives the $BH_4^-$ preferential access to the *si* face of the ketone for delivery of hydride (indicated by an arrow from one $BH_4^-$ hydrogen to the carbonyl carbon of **4**), yielding the (*S*)-alcohol. This figure was prepared using Chem3D (Cambridgesoft, Inc.).

the model reaction (Table 1). In retrospect, this result is not surprising, since only one site can be blocked at a time by the naphthyl ring, and there is no obvious structural reason the V site should be preferentially blocked relative to the OH site. However, catalyst **3a** derived from 9-chloromethylanthracene gave a significant increase in ee relative to catalyst **1a** (from 21% to 30% ee), suggesting that our structure-based analysis was correct.[8b]

**Comparison of Solution Conformations of NAQ and NBQ and Ion-Pair Structures of $NAQBH_4$ and $NBQBH_4$.** We next characterized the solution structure of the $NAQBH_4$ ion pair **3b** in order to determine whether the predicted changes in relative anion occupancies of the OH and V sites in fact took place. A comparison of the energy-minimized structures of the NBQ **1** and NAQ **3** cations show that they are very similar (Figure 4). In both cases, the quinoline ring is twisted out of the plane defined by the aromatic substituent of the quaternary nitrogen. Observed NOEs support the conformations shown for both cations. NOEs obtained from ROESY spectra of $NAQBH_4$ **3b** indicate the anthryl ring is positioned with respect to the quinuclidine so that the anthryl protons 25 and 33 are equidistant on a time average from the quinuclidine protons 18 and 16, respectively, and also to methylene protons 24 and 23, respectively. Consider the plane defined by the anthryl ring situated in the above manner with respect to the quinuclidine ring: The quinoline ring must be rotated out of plane to explain the presence of NOEs between proton 5 on the quinoline ring and protons 8, 9, and 24 (Figure 4). No NOEs are observed for either NBQ or NAQ that suggest significant populations of any other conformation for the quinoline ring than that shown (see Figure 4).

A comparison of the interionic NOEs observed in ion pairs $NBQBH_4$ **1b** and $NAQBH_4$ **3b** shows clearly that

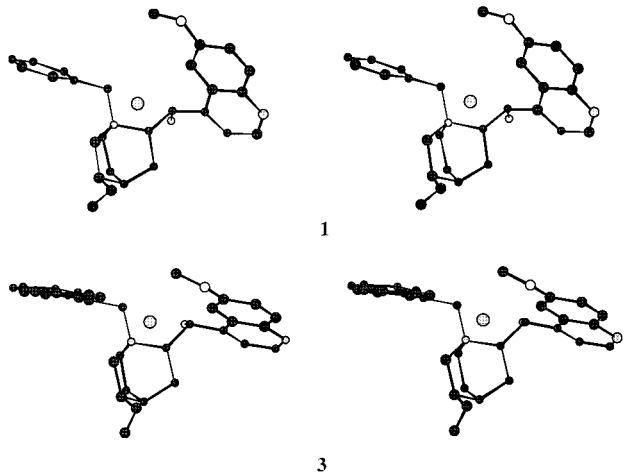



**Figure 4.** Stereoviews of MOPAC (PM3)-minimized structures for the NBQ **1** and NAQ **3** cations (protons not shown). A counterion is shown occupying the V site (see Figure 2), but was not present during the MOPAC calculation (see text). This figure was prepared using Chem3D (Cambridgesoft, Inc.).

occupancy of the OH site relative to the V site is larger in $NAQBH_4$ **3b** than in $NBQBH_4$ **1b**, as predicted from the model in Figure 2. These NOES are shown in Figure 5 and summarized in Table 2. As noted above, relative NOE intensities indicate approximately equal occupancies for both the OH and V sites in $NBQBH_4$ **1b**. However, in the $NAQBH_4$ ion pair **3b**, NOEs between $BH_4^-$ and cationic protons 33, 23, 16, and 8 (all of which indicate anion occupancy of the OH site) are approximately double the intensity of those NOEs that indicate the presence of $BH_4^-$ at the V site (those being interionic NOEs between $BH_4^-$ and protons 25, 24, 18, and 9; see Table 2). On the basis of these observations, the $BH_4^-$ is twice

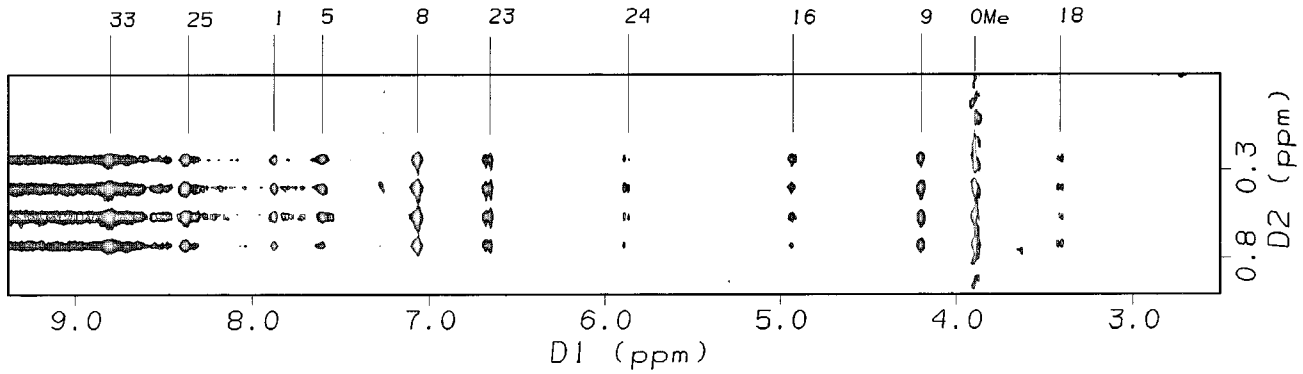



**Figure 5.** Portion of a contour plot of a 500 MHz ROESY spectrum of $NAQBH_4$ **3b** showing the NOE cross-peaks between $BH_4^-$ protons and protons on NAQ cation ($CDCl_3$, 0.08 M, 298 K). The spectrum was obtained using a 200 ms 2.5 kHz spin-locking pulse. The horizontal axis (labeled D2) shows the region of the spectrum containing the resonance of the $BH_4^-$ protons, which is split into a 1:1:1:1 quartet by a 90 Hz $^1J_{BH}$ coupling to the quadrupolar $^{11}B$ ($\mathbf{I} = 3/2$, four spin states) Numbering of resonances along the D1 axis corresponds to proton numbering in Figure 1.

as likely to occupy the OH site than the V site in the NAQ cation **3**.

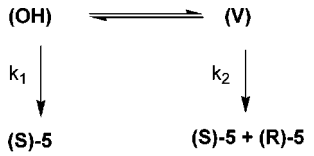
Although it is difficult to compare absolute NOE intensities between different experiments, interionic NOEs in $NAQBH_4$ were in general weaker than those observed for $NBQBH_4$. At first, this was taken as evidence that the ion pairs formed by NAQ were looser than those formed NBQ. However, NMR diffusion measurements for $NBQBH_4$ and $NAQBH_4$ indicate that both cation and anion in a given ion pair diffuse at the same rate. This shows that the ion pair is diffusing as a single species and, hence, is a tight ion pair.[16] A comparison of the diffusion coefficients for 0.008 M solutions of $NBQBH_4$ **1b** and $NAQBH_4$ **3b** show, as expected, that $NBQBH_4$ **1b** diffuses at a slightly greater rate, $(6.75 \pm 0.06) \times 10^{-6}$ $cm^2/s$, than does $NAQBH_4$ **3b** $(6.47 \pm 0.15) \times 10^{-6}$ $cm^2/s$. It is possible that the generally lower intensities of the interionic NOEs in $NAQBH_4$ relative to $NBQBH_4$ are the result of the expected overall increase in the steric barriers to close approach of the anion to the cation caused by the introduction of the anthryl group.

The other major difference between the NBQ **1** and NAQ **3** is that the ring flip for the phenyl group of the NBQ cation is fast on the chemical shift time scale. Protons 25 and 29 are equivalent, as are protons 26 and 28 at 298 K for **1a** and **1b**. In NAQ **3**, all of the anthryl protons are nonequivalent. A 4 s saturation of proton 33, which is well separated from other proton resonances, showed no effect in the signal intensity of proton 25 in the anthryl ring, indicating that no significant saturation transfer is occurring on the time scale of the experiment. Thus, the anthryl ring does not reorient rapidly on either the chemical shift or $T_1$ time scales.

## Discussion

We now attempt to rationalize our observations concerning the model reaction shown in Scheme 1 and the NMR structures of the ion pairs formed by $NBQBH_4$ **1b** and $NAQBH_4$ **3b**. To summarize experimental data, we have found that upon replacement of catalyst **1a** with **3a** in the model reaction, the ee increased from ~21% to 30%, with the (*S*)-enantiomer of alcohol **5** in excess (Table 1). We also note that the relative populations of $BH_4^-$ in

**Scheme 2**




the two anion-binding sites differ between $NBQBH_4$ **1b** and $NAQBH_4$ **3b**. In the case of **1b**, the OH and V sites are populated approximately 1:1 based on relative integrations of interionic NOEs characteristic of the two sites. In the case of $NAQBH_4$ **3b**, the $BH_4^-$ population of the OH site is twice that of the V site. Together, these observations can be fit to a kinetic model that successfully predicts the extent of change in asymmetric induction observed as a function of relative populations of the two anion-binding sites in the catalyst (see Scheme 2). In this model, the $BH_4^-$ bound in OH site is responsible for all asymmetric induction, consistent with experimental evidence.[10,15] We make the further simplification that only one enantiomer of **5**, (*S*)-**5**, is produced at the OH site (i.e., that this site contributes exclusively to the production of the alcohol enantiomer found in excess), and that the production of (*S*)-**5** at the OH site is governed by a rate constant $k_1$. Ketone reduction at the V site is assumed to result in equal amounts of both enantiomers of **5**, and the rate constant governing the production of each enantiomer (obviously the same for both) is $k_2$. The differential rate expressions for the formation of each enantiomer are then given by

$$\frac{d(S)}{dt} = k_1[OH] + k_2[V] \quad (1)$$

$$\frac{d(R)}{dt} = k_2[V] \quad (2)$$

where [V] is the concentration of $BH_4^-$ in the V site and [OH] the concentration of $BH_4^-$ in the OH site (all concentrations are in arbitrary units). Although absolute rates have not been measured for the reaction in Scheme 1, it is possible to obtain relative rates of formation of the two enantiomers of **5**: Because the reduction is irreversible, the mole fraction of each enantiomer in the product is proportional to the rate at which that enantiomer is formed. In the case of the reaction catalyzed by NBQCl **1a**, the relative rates of formation of (*S*)-**5** to

(16) Mo, H.; Pochapsky, T. C. *J. Phys. Chem. B* **1997**, *101*, 4485–4486.

(*R*)-**5** (*S*/*R*) are ~3:2 (20% ee). Substitution of these relative rates into eqs 1 and 2, along with equal values of [V] and [OH] (reflecting the ~1:1 ratios of NOE intensities used to establish occupancies of anion binding sites in **1b**) gives

$$\frac{d(S)}{dt} = 3 = k_1[1] + k_2[1] \quad (3)$$

$$\frac{d(R)}{dt} = 2 = k_2[1] \quad (4)$$

which can be easily solved to give $k_1 = 1$, $k_2 = 2$.

If the population of the OH site is doubled relative to the V site, as is observed for **3b**, i.e., [OH] = 2[V], using the same rate expressions and rate constants, one obtains

$$\frac{d(S)}{dt} = 4 = k_1[2] + k_2[1] \quad (5)$$

$$\frac{d(R)}{dt} = 2 = k_2[1] \quad (6)$$

The model thus predicts relative rates of formation of *S*/*R* of 4:2 using **3a** as a catalyst for the reaction in Scheme 1. This corresponds to an ee of 33%, only slightly larger than the 30% actually observed using **3a** as a catalyst (Table 1).

A number of other assumptions are implicit in this kinetic model. First, it is assumed that ion pairs $NBQBH_4$ **1b** and $NAQBH_4$ **3b** represent the reactive species in the phase-transfer reductions catalyzed by the chloride salts **1a** and **3a**, respectively. Because **1a** and **3a** are added only in catalytic amounts to the reaction (Table 1), $BH_4^-$ is present in large excess to $Cl^-$, so this is a reasonable assumption. Second, it is assumed that $BH_4^-$ remains paired with the catalytic cation throughout the reaction process (i.e., $BH_4^-$ free in $CHCl_3$ solution is not an important contributor to the reaction) and that the hydride-transfer step is fast relative to the rate at which anions exchange from one site to another. This also is reasonable, since the hydride transfer is a bond-making/breaking step (on the order of a bond vibrational lifetime), while the lifetime of a discrete ion-binding mode in a closed shell ion pair of this type is many orders of magnitude longer.[6c,e] It is also assumed that $BH_4^-$ is the only reducing species; that is, mixed alkoxy hydroborates are not important reducing agents in this reaction. This seems unlikely at first in light of kinetic evidence suggesting that transfer of the first hydride is the rate-determining step in $BH_4^-$ reductions.[17a,b] However, House has pointed out that the same kinetics can be explained by a rapid disproportionation of the mixed alkoxy hydroborates to regenerate $BH_4^-$, such that the actual reducing agent is always $BH_4^-$.[18] We have found that the observed ee for the reaction shown in Scheme 1 does not change over the course of the reaction (which takes several hours to go to completion under the conditions described here), supporting the notion that mixed alkoxy hydroborates (which should change in concentration with the extent of reaction) are either unimportant or else do not change the enantioselectivity appreciably. Similarly, neither the $BH_4^-$:ketone ratio or the catalyst concentration have any appreciable effect on the stereochemical outcome of the reduction. These observations all indicate that $BH_4^-$ is the only reducing agent present in significant concentrations under the reaction conditions of Scheme 1.

One conclusion that can be drawn from the kinetic analysis presented here is that, at least in theory, much higher ees are possible than what have been observed to date for phase-transfer reductions of prochiral ketones with $BH_4^-$ if improved blocking of the V site can be accomplished. We are continuing to attempt to synthesize quinine-based phase-transfer catalysts with the V site blocked more or less completely. However, even the 30% ee for the reduction of **4** obtained using catalyst **3b** is equal to the best reported ee for such phase-transfer reductions in the literature.[19] We chose the reaction in Scheme 1 primarily for ease of monitoring ee (the enantiomers of **5** are well resolved on Pirkle-type chiral stationary phases). We have not as yet investigated how effective catalyst **3b** is for the asymmetric reduction of other ketones.

The current work demonstrates that structural information concerning the active species in PTC (that is, the ion pair) can be used in the design of more effective phase-transfer catalysts. Although the asymmetric induction observed for the reaction shown in Scheme 1 does not reach the level of a useful synthetic tool, the net improvement in the asymmetric induction and the agreement between the predicted and observed outcomes of the catalyst modifications in terms of ion site occupancy accentuates the importance of structural information for rational catalyst design. Furthermore, the success of anthrylated chinchona PTCs for other applications suggests that catalysts designed for one type of reaction may have unexepected benefits for other reactions as well.[3b,c]

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