Full Paper

Israel Journal of Chemistry

DOI: 10.1002/ijch.201700112

An Exploration of Induced Supramolecular Chirality Through Association of Chiral Ammonium Ions and Tartrates with the Achiral Host Cucurbit[7]uril

Wenjing Wu,[a] Michael P. Cronin,[a] Lynne Wallace,[a] and Anthony I. Day*[a]

Abstract: The chiral amines (R,R and S,S)-1-amino-2-benzyloxycyclopentane and (R and S)-α-methylbenzylamine were converted to ammonium (D and L) hydrogen tartrate salts and induced chiroptic effects were investigated following encapsulation in Q[7]. Significant chiroptic differences were observed in ORD and CD spectra for the two amines. The optical spectra were performed as a precursor study to a potential method for enantiomer separation, utilising Q[7] encapsulation in conjunction with enantio-pure hydrogen tartrates. An enantiomeric excess was achieved for the two antipodes of 1-amino-2-benzyoxycyclopentane but not for those of α-methylbenzylamine. However, material differences of crystallinity or the formation of a glass were observed for the latter amine induced by the different antipodes of hydrogen tartrate. ^{1}H NMR spectra of aminobenzyloxycyclopentane showed back-folding of the two rings with complete encapsulation in Q[7], leading to a secondary helical structure observed in CD spectra.

Keywords: supramolecular chirality · cucurbituril · chiral guest encapsulation · induced chirality

1. Introduction

Important industrial processes for the synthesis of ingredients and products with chiral activity are restricted by cost and physical limitations imposed by the requirement for large scale.[1–4] These limitations then determine the choices available for the most efficient route to a product, whether it is through asymmetric synthesis, the separation of enantiomeric mixtures or a combination of both. One of the most cost effective approaches to the efficient synthesis of pure chiral commercial products is the utilization of synthetic procedures involving enantio-pure reagents or precursors at a critical step during synthesis. Many relatively small synthetic molecules that could be applicable to this purpose are racemic and therefore require bulk methods to separate out the desired enantiomer. A method frequently practiced by industry for large-scale purification involves a crystallisation process using a chiral auxiliary agent.[1,5,6] Some important examples of chiral auxiliary agents in use are the pure racemates of tartaric acid and a number of tartaric acid derivatives.[2,5,6] These agents are relatively inexpensive, available in large quantities and are non-toxic.

One group of molecules of particular interest as chiral precursors are amines, which have become increasingly important to industry in their use as defined enantiomers in pharmaceuticals, agrochemicals and chemical product synthesis. Numerous chromatographic methods are available and these are constantly being improved as they are of primary importance as analytical methods for R&D,[1,7–9] and in situations of no choice are used for bulk chiral separation. Recent improvements in larger scale chiral separations using supercritical fluid chromatography[3] look promising for future choices as do chiral phase transfer agents[10] or ion exchange[11] but chiral separation by crystallisation will also remain as a significant method while it provides the lowest cost choice.

With advances in supramolecular chemistry, especially host-guest chemistry, the preparation and separation of chiral compounds has also been a significant research topic for chiral hosts and achiral hosts.[12,13] The subject of this report is the use of the achiral molecular host, cucurbit[7]uril (Q[7]) as a potential tool for the separation of chiral amines by enhancing the separation properties of an auxiliary chiral agent in crystallisation. We report a preliminary exploration towards a proof of concept, combining the chiral crystallisation selectivity of an optically pure tartrate and encapsulated racemic ammonium salts.

Yuan et al in 2007, reported the formation of chiral supramolecular structures via encapsulation of the pure enantiomers of an ammonium naphthyl derivative in Q[7] and were the first to demonstrate a chiroptic effect of spectroscopic enhancement and band changes relative to the free ammonium naphthyl derivative.[14] However, given that only a single example was reported, the generality of this phenomenon to chiral molecules encapsulation in Q[*n*] was not certain. As such, part of our objective was to investigate two additional examples for chiroptic changes. Our approach was first to

[a] W. Wu, M. P. Cronin, L. Wallace, A. I. Day
Chemistry, School of PEMS, University of New South Wales Canberra, Australian Defence Force Academy, Canberra, ACT 2600, Australia
E-mail: a.day@adfa.edu.au

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ijch.201700112

examine the encapsulation of enantio-pure ammonium salts, and then secondly, to add a chiral auxiliary external to the cavity but as an integral component in the supramolecular structure to determine the effect. From this it was anticipated that the optical spectral changes (CD or ORD), would provide an insight into the potential influence of a chiral auxiliary. The final test of the chiral influence of the auxiliary in this study was crystallisation with the objective of achieving an enantiomeric excess controlled by the auxiliary and hopefully enhanced by the Q[7].

2. Results and Discussion

To undertake this study the chiral properties of the combination of two enantio-pure ammonium salts of (R,R and S,S)-1-amino-2-benzyloxycyclopentane (R or S-ABC$^+$, the meso was not included in the study, Figure 1) and (R and S)-α-methylbenzylamine (R or S-MBA$^+$) encapsulated in Q[7] were established by recording their ORD and CD spectra. This was expected to demonstrate whether these combinations would follow the phenomena previous reported[14] and if not what could we learn from the differences.

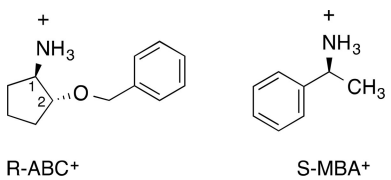


Figure 1. Representative enantiomers of the two chiral ammonium salts ABC$^+$ and MBA$^+$.

The first steps, were to verify that an observable effect by ORD and/or CD could be measured for ammonium salts as chlorides of R- or S-ABC$^+$ and R- or S-MBA$^+$, then as the next step, the chloride ion was replaced by L and D hydrogen tartrate ions (L- or D-HT$^-$) for each enantiomer in turn, for R- or S-ABC$^+$ and R or S-MBA$^+$ and to measure the induced chiroptic effects. This information was intended to help to determine whether a chiral anion such as HT$^-$ had the potential to act as a chiral auxiliary in a crystallisation process for the separation of a racemic amine with Q[7] as a facilitator.

2.1 Optical Rotary Dispersion Spectra (ORD)

The ORD spectra recorded as molar optical rotations at 436 and 546 nm for each of the enantiomers of ABC$^+$ as their chloride salts, gave a significant chiroptic effect. At both wavelengths as the proportion of Q[7] was increased to a mole ratio of 1:1, the molar rotation decreased ~20 fold (Figure 2, and SI, Figure S1 for $[M]_{546}$). The only difference between the

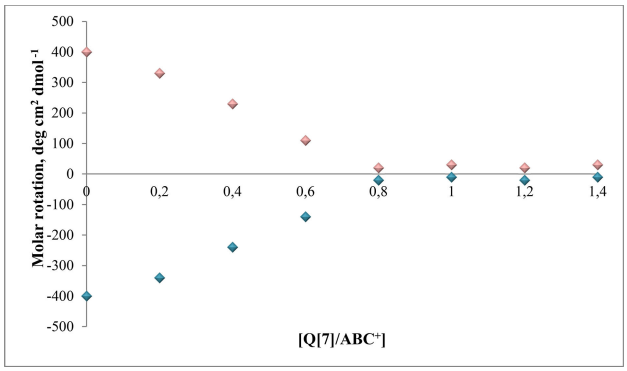


Figure 2. The relative change in molar optical rotation $[M]_{436}$ at different ratios of [Q[7]]/ABC$^+$] in aqueous solution at 20 °C for (blue) R-ABC$^+$ Cl$^-$ and (orange) S-ABC$^+$ Cl$^-$ at 2 mM.

two wavelengths was that the shorter wavelength gave more intense initial molar rotations, otherwise the response to Q[7] additions gave a similar trend. Significantly the decrease in molar rotation of ABC$^+$ with increasing proportion of Q[7] is in contrast to the response of the previously reported chiral naphthyl derivative which was shown to increase with increasing proportions of Q[7]. [14]

An attempt to conduct a similar experiment with R- or S-MBA$^+$ chloride salt was restricted by limited solubility as the Q[7] was added, and significantly smaller molar rotations at 2 mM. However, this problem was not relevant when the Cl$^-$ ion was replaced by either L- or D-HT$^-$. In this case the ORD spectra of R- or S-MBA$^+$ and L- or D-HT$^-$ salts were recorded with the addition of Q[7]. The result was indicative of two supramolecular diastereomeric forms where in one form R-MBA$^+$ L-HT$^-$ and S-MBA$^+$ D-HT$^-$ (the positive [+ve] and negative [−ve] respectively) the molar rotations increase (more +ve and −ve) as the ratio of Q[7] was increased (Figure 3a). Precipitation begins to occur beyond a mole ratio of 0.9. In contrast, the alternative diastereomeric form R-MBA$^+$ D-HT$^-$ and S-MBA$^+$ L-HT$^-$ (+ve and −ve respectively) the molar rotations decrease (less +ve and −ve) as the ratio of Q[7] was increased (Figure 3b). In this latter case precipitation occurred beyond a mole ratio of 1.1.

In comparison, the two supramolecular 'racemic forms' of R-ABC$^+$D-HT$^-$/S-ABC$^+$L-HT$^-$ and R-ABC$^+$L-HT$^-$/S-ABC$^+$ D-HT$^-$ with addition of Q[7] show a regular decrease in molar rotation for the former, with convergence near zero and a more complex change for the latter (a and b respectively). The R-ABC$^+$L-HT$^-$/S-ABC$^+$D-HT$^-$ combinations shown in Figure 4b indicate a decrease in the magnitude of the molar rotations and a convergence to zero at a mole ratio of ~0.75 with addition of Q[7]. At a higher ratio of Q[7] the sign of the molar rotations are reversed reaching a maximum at a mole ratio of 1.2. These combinations S-ABC$^+$L-HT$^-$/R-ABC$^+$D-HT$^-$ and S-ABC$^+$D-HT$^-$/R-ABC$^+$L-HT$^-$ (Figure 4a and b respectively) could be designated as supramolecular antipodes on the basis of their reflected ORD behaviours. Curiously, the initial ORD molar optical rotations of S-ABC$^+$L-HT$^-$/R-

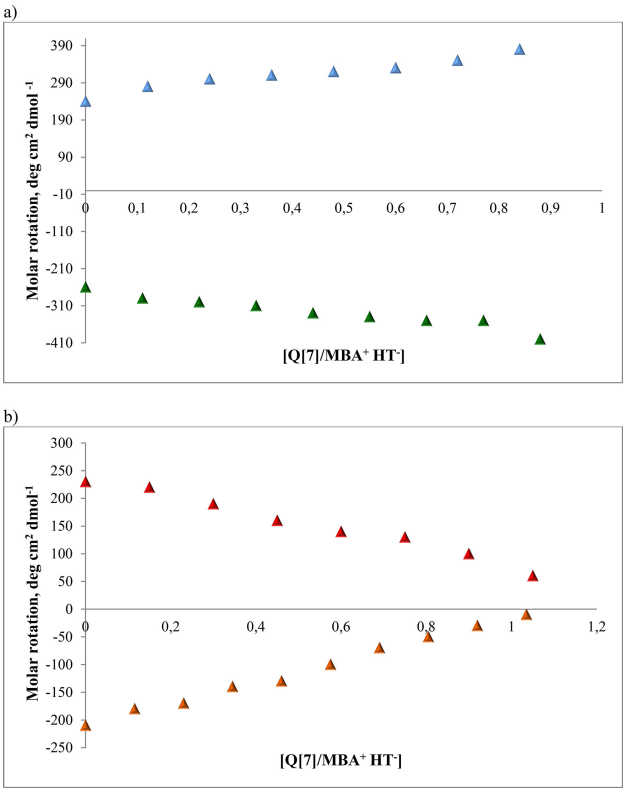


Figure 3. The relative change in molar optical rotation $[M]_{436}$ at different ratios of [Q[7]/MBA^+ HT^-] in aqueous solution at 20 °C for, a) (green) R- MBA^+ L-HT^- and (blue) S- MBA^+ D-HT^-; and b) (red) R-MBA^+ D-HT^- and (orange) S-MBA^+ L-HT^- . All at 2 mM.

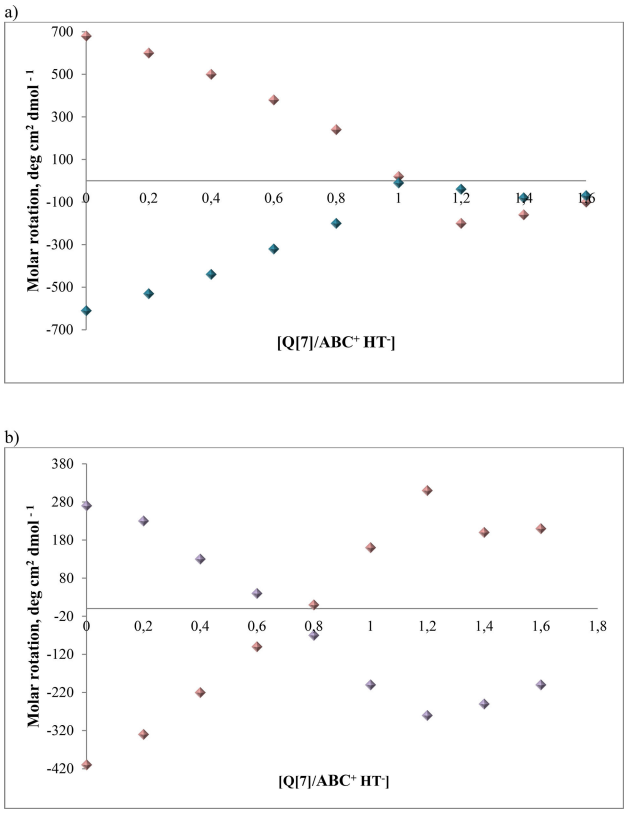


Figure 4. The relative change in molar optical rotation $[M]_{436}$ at different ratios of [Q[7]/ABC^+ HT^-] in aqueous solution at 20 °C for, a) (pink) S-ABC^+L-HT^- /(blue) R-ABC^+D-HT^- ; and b) (yellow) S-ABC^+D-HT^- /(pink) R-ABC^+L-HT^-. All at 2 mM.

ABC^+D-HT^- (680 and - 610 respectively, Figure 4a) were not equivalent. However, each of the individual components was verified to be equiv. prior to HT^- salt formation (as an example see Figure 2). Significantly the initial molar optical rotations of the combinations S-ABC^+D-HT^- /R-ABC^+L-HT^- were substantially different (270 and −410 respectively). Consequently these combinations are significantly different in their CD spectra as well (see SI, Figure S9).

Small differences in the initial molar optical rotation ORD points for the combinations of MBA^+HT^- (no Q[7]) were $<10\,\%$, far less significant than the ABC^+ HT^- combinations. The differences may indicate a pairing of ammonium tartrate salts under aqueous conditions even before the addition of Q[7].[15]

There are clear differences between the two racemic forms of both the Q[7]]/MBA^+ HT^- sets and the Q[7]]/ABC^+ HT^-] sets. It was anticipated that these differences could indicate that separation may have a chance.

By ^{1}H NMR each combination of ABC^+@Q[7] and MBA^+@Q[7] showed spectra where all protons attached to carbon were encapsulated within the cavity of Q[7] with clearly defined upfield shifted proton resonances. The exchange kinetics on the NMR timescale were moderate, with no definable free and bound guest resonances only averages with maximum attainable upfield shifts at 1 : 1 (Q[7]: guest). MBA^+@Q[7] in particular showed relatively sharp coupling for the guest proton resonances and a clear differentiation of the aromatic protons centrally located within the cavity (between 0.62–0.9 ppm, SI, Figure S16). A binding constant was established for MBA^+@Q[7] by adding portions of Q[7] to a D_2O solution of R-MBA^+D-HT^-. The clearly defined upfield shift difference of the CH_3 proton resonances was plotted against [Q[7]/MBA] and curve fitted as a 1 : 1 complex (10^6 M^{-1}, SI).

The establishment of a binding constant for R-ABC^+ @Q[7] was not as accessible by ^{1}H NMR as the proton resonances were not as clearly definable until close to 1 : 1 binding. However, a binding constant was established for this association complex by using a curve-fitting model applied to the data obtained from the ORD titration of Figure 2. Consistent with its ^{1}H NMR and the ORD a 1 : 1 binding model was assumed, which gave an approximate K_a of 10^5 M^{-1} indicating that ABC^+ and MBA^+ have similar binding constants (SI, Figure S3).

As mentioned above all protons attached to carbon on either MBA^+ or ABC^+ had upfield shifted resonances when encapsulated in Q[7]. This was anticipated for MBA^+ but was surprising in the case of ABC^+. In the latter example, this

indicates that both rings are cavity bound requiring a fold-back to allow cavity accommodation (Figure 5). In addition, an examination of the chemical shift differences between the resonances of free R-ABC$^+$ D-HT$^-$ and R-ABC$^+$@Q[7] D-HT$^-$ reveals that not only are all C–H's shifted upfield but that the methylene protons at C-3 of the cyclopentane, show unusually large upfield shifts of 1.5 and 1.7 ppm (SI, Table S2, Figure S12). A central cavity location, plus a shielding effect as a consequence of proximity to the centre of the phenyl ring is consistent with a back-folding arrangement. The modeled structure shown in Figure 5, correlates well with the small shift for the CH–N (0.08 and ppm) where the NH_3^+ sits at the portal and the relatively smaller shift for the para H–Ar compared to meta and ortho supporting its location near the opposite portal (0.47, 0.61 and 0.89 respectively). Also the benzyl CH_2 as diastereotopic protons, were substantially differentiated in their individual chemical shifts, consistent with one pointing toward the geometric centre of the cavity and the other toward the portal (1.08 and 0.29 respectively). The NOESY spectrum also supports the fold-back with strong cross correlations between the ortho-Ar protons and CH_2 protons of C-3 (SI, Figure S13 and S14). The structural representations shown in Figure 5, were derived through modelling. This was achieved by first orientating the two rings of the ABC$^+$ molecule in a fold-back state consistent with the NOESY correlations. Then the back-folded ABC$^+$ was placed in the cavity of Q[7] with the NH_3^+ located near a portal and the structure minimised.[16] The minimised model was found to be also consistent with ^{1}H NMR chemicals shifts relative to cavity depth (complete table of chemical shifts SI, Table S2).

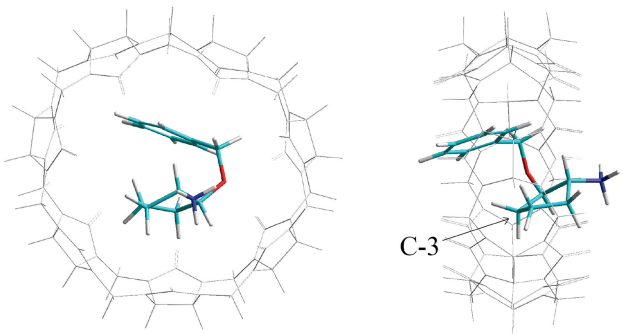


Figure 5. A portal view of Q[7] showing the two rings of ABC$^+$ back-folded (LHS) and a side view of ABC$^+$ showing the relative arrangements of the two rings to each other and highlighting C-3's proximity to the centre of the phenyl ring (RHS).

By ^{1}H NMR it has been established that both MBA$^+$ and ABC$^+$ were fully encapsulated within the cavity of Q[7] but the association of HT$^-$ can only be tentatively determined to have close proximity to the portal. HT$^-$ as the counterion to either ABC$^+$ or MBA$^+$ shows only a very small downfield shift of <0.1 ppm, which may indicate a weak association.

Carboxylic acid binding to Q[7] has been reported as significant but upon deprotonation forms the carboxylate ion at which point binding becomes unfavourable.[17–24] However, there are at least two circumstances where the repulsion of the negative $-CO_2^-$ ion by the electronegative portal is limited. These are when there is a zwitterion as in amino acids or a pseudozwitterion such as $-CO_2^-$ and pyridinium ions in the same molecule.[23,24] In consideration of these conditions it was anticipated that the HT$^-$ ion in conjunction with an ammonium ion located within a portal could operate in a similar fashion. This was also rationalised by considering a portal association that would be facilitated by the remaining CO_2H and two OH groups of the HT$^-$ ion, which would H-bond to the portal.

The ORD of D-tartaric acid at 436 and 546 nm was recorded following incremental additions of Q[7] up to a mole ratio of 1.4 : 1 (Q[7] : D-tartaric acid) and this showed changes in the molar rotation in an increasing positive direction which plateaued at 1 : 1 (SI, Figure S4). A curve-fitted model indicated that an approximate K_a for (tartaric acid)@Q[7] $\sim 10^7$ M^{-1} assuming a 1 : 1 binding. The mode of binding for tartaric acid is assumed to be portal as there are no shifted resonances by ^{1}H NMR with the addition of Q[7]. The lack of a downfield shift may only be indicative of a high exchange rate (generally portal interactions give only small shifts even for slower exchange rates).

In this study the HT$^-$ is relevant and to test this for portal association the influence of a chiral guest@host was removed, while maintaining the possible relationship to a bound NH_3^+ and the portal. This was achieved in the form of the achiral benzyl ammonium ion together with the hydrogen tartrate ($BzNH_3^+$ D-HT$^-$), which was compared in the absence and presence of Q[7]. The ORD showed a small positive increase in the molar rotation (40 deg cm^2 dmol^{-1}) at 436 nm, following the addition of Q[7] but this was not as significant as the change found for tartaric acid discussed above. Further evidence to this point is discussed in the subsequent text below.

2.2 Circular Dichroism Spectra (CD)

In addition to ORD the CD spectra were also recorded in order to further evaluate the potential for the use of Q[7] as a tool for enantiomeric separation.

CD was also used to further investigate the question of an association of the HT$^-$ ion with an internally bound portal ammonium ion, which could have ion-ion interaction together with secondary portal binding to the CO_2H and OH groups as H-bonding. In the case of the achiral guest $BzNH_3^+$ and D-HT$^-$ the CD spectra showed a slight decrease by 7 deg M^{-1} cm^{-1} for $BzNH_3^+$@Q[7] D-HT$^-$ (IS, Figure S7). This change suggest that the D-HT$^-$ ion does associate with the portal and the cavity bound ammonium ions to form chiral supramolecular species.

Focusing then on the chiral cavity bound guests the CD spectra revealed significant differences between the free guest R- or S-MBA$^+$ HT$^-$ and (R- or S-MBA$^+$)@Q[7] HT$^-$. In the case of R-MBA$^+$ D-HT$^-$ and R-MBA$^+$L-HT there was a reduction in magnitude of the molar ellipticity without a change in the sign following encapsulation. In addition, the minima was blue shifted by >3 nm (SI, Figure S8). Comparing S-MBA$^+$D-HT$^-$ and S-MBA$^+$L-HT$^-$ free and encapsulated in Q[7] revealed the significant reduction in magnitude of the molar ellipticity of S-MBA$^+$L-HT$^-$ as a consequence of Q[7] association. S-MBA$^+$D-HT$^-$ in contrast only resulted in a small blue shift (3 nm) and no change in intensity (Figure 6).

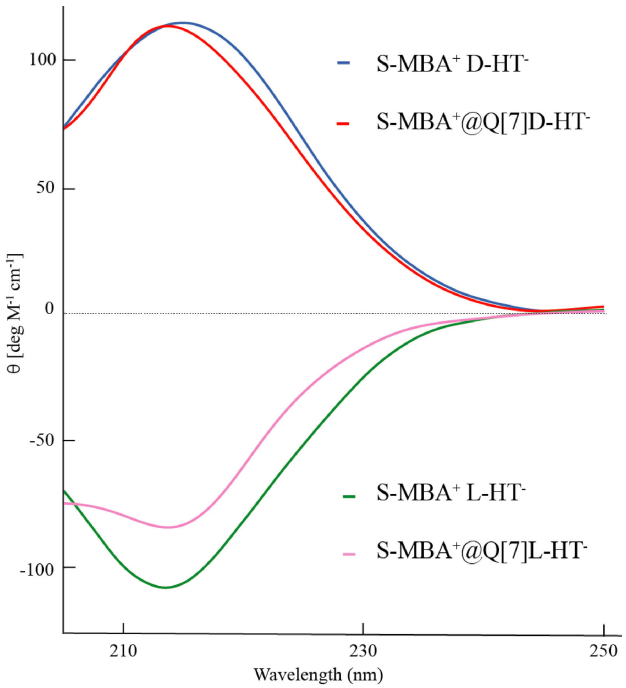


Figure 6. The CD spectra of free as S-MBA$^+$ (D-HT$^-$ or L-HT$^-$) and the encapsulated forms S-MBA$^+$@Q[7] D-HT$^-$ and S-MBA$^+$@Q[7] L-HT$^-$ in water 1.5 mM.

Distinguished from the above example, adding 1 equiv. of Q[7] to R-ABC$^+$ and S-ABC$^+$ as Cl$^-$ salts, showed a pronounced change in their CD spectra. An inversion of the sign of ellipticity for each enantiomer and an enhancement to give a maxima for R-ABC$^+$ @Q[7] and an enhanced minima for S-ABC$^+$@Q[7], each mirrored at 218 nm (Figure 7). A small red shift (4 nm) also occurred relative to ABC$^+$ in the absence of Q[7].

CD spectra of the combinations of R-ABC$^+$D-HT$^-$/S-ABC$^+$L-HT$^-$ and S-ABC$^+$D-HT$^-$/R-ABC$^+$L-HT$^-$ were then compared. To each of these combinations Q[7] was added at a ratio of 1:1(SI, Figure S9). Close examination of the CD spectra after Q[7] was added led to two interesting observations. The combination S-ABC$^+$@Q[7] D-HT$^-$ showed a positive ellipticity with two maxima at 212 and 226 nm ([θ] +35 and +26 respectively). Reflected in character but not in intensity was a CD spectrum of R-ABC$^+$@Q[7] L-HT$^-$ with a negative ellipticity and negative minima at 212 and 227 nm ([θ] −53 and −21 respectively) as shown in Figure 8a. In contrast, the combinations R-ABC$^+$@Q[7] D-HT$^-$ and S-ABC$^+$@Q[7] L-HT$^-$ gave mirrored CD spectra but with single absorption bands at 215 nm ([θ] +136 and −136, Figure 8b).

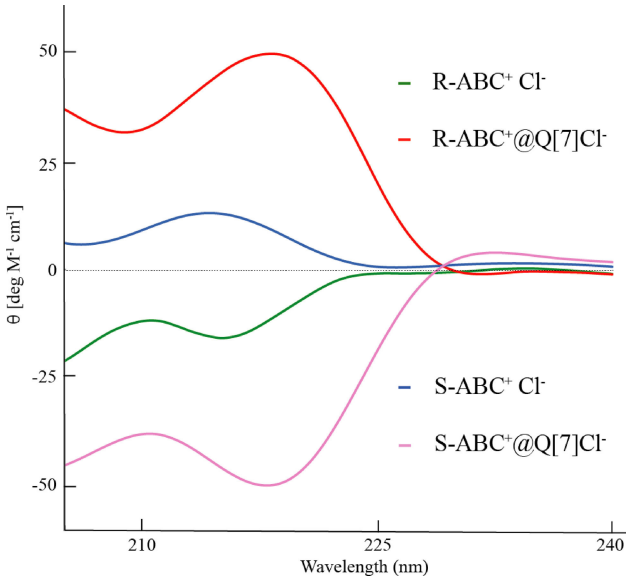


Figure 7. The CD spectra comparing free R- or S-ABC$^+$ as the Cl$^-$, to encapsulation in Q[7] at a ratio of 1:1.

The two enantiomers R- and S- ABC$^+$@Q[7] HT$^-$ adopt helical arrangements in opposite directions as a consequence of the complete cavity encapsulation and back-folding of the two rings (SI, Figure S14). The relative orientation of the two back-folded rings together with the relative twist left or right, is supported by the cross correlation found in NOESY spectra previously discussed. The phenyl ring is offset to the cyclopentyl ring where the centre of the phenyl ring sits above C-3 of the cyclopentyl ring.

The features of the CD spectral bands, especially those of Figure 8a, may indicate some secondary structure effects of the twist in the supramolecular forms S-ABC$^+$@Q[7] D-HT$^-$ and R-ABC$^+$@Q[7] L-HT$^-$. The alternative combinations shown in figure 8b have featureless curves.

The data obtained from both ORD and CD spectra suggested that Q[7] with encapsulated chiral ammonium guest exhibits a significant association with a chiral anion such as HT$^-$. The question then was, can this association be used as a method for the separation of enantiomeric mixtures and would Q[7] provide any advantage?

2.2 Crystallisation Toward Enantiomeric Excess

One of the objectives in this process of the separation of racemic mixtures using the auxiliary HT$^-$ was intended as an

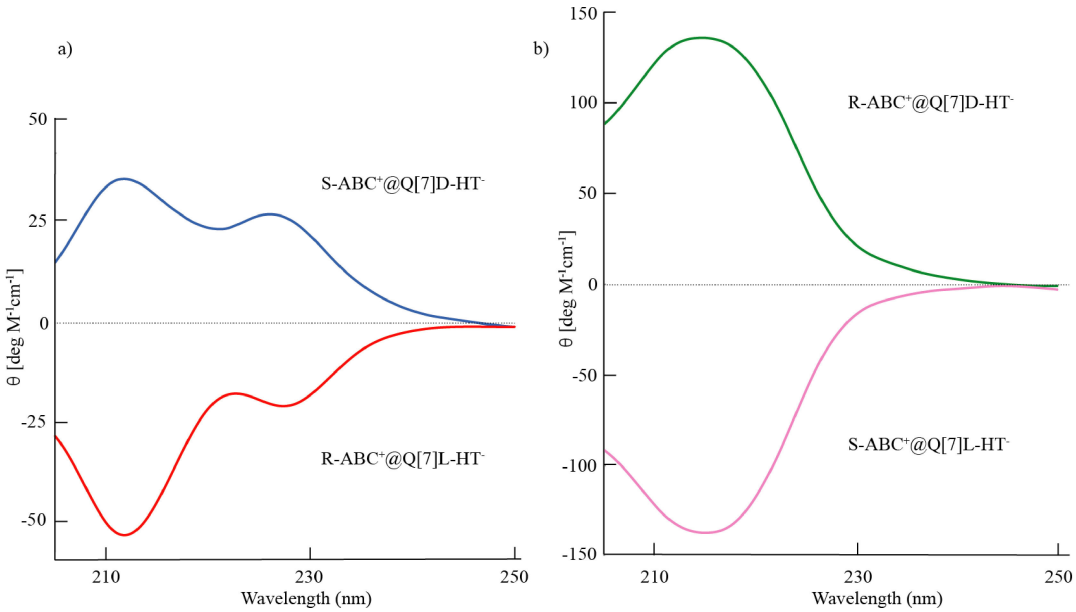


Figure 8. CD spectra comparing the four combinations of enantiomers of ABC^+@Q[7] HT^-. a) The near mirrored pair S-ABC^+@Q[7] D-HT^- and R-ABC^+@Q[7] L-HT^-. b) The alternative mirrored pair R-ABC^+@Q[7] D-HT^- and S-ABC^+@Q[7] L-HT^-.

aid in a crystallisation in water, as a green approach to the purification of enantiomers. Racemic mixtures of MBA^+ and ABC^+ were prepared as HT^- salts in water and Q[7] was added to give a final mole ratio of 1 : 1 : 1. It was found that the complexes MBA^+@Q[7](D-HT^- or L-HT^-) were highly soluble in water and were very resistant to crystallisation. ABC^+@Q[7](D-HT^- or L-HT^-) also had high solubility in water but crystals were obtained. The crystals obtained from a single crop of the ABC^+ complex were shown by ^{1}H NMR to contain the three components as in the original ratio of 1 : 1 : 1. However, the combination with D-HT^- as the anion gave R-ABC^+ with an ee of 33 % whereas the alternative anion L-HT^- gave S-ABC^+ with an ee of 12 %. Curiously these crystalline forms correspond to the mirrored pair in Figure 8b.

The intention in these experiments was to demonstrate a proof of concept and therefore recrystallisation was not investigated for optimisation. Attempts to initiate crystallisation of MBA^+@Q[7]D-HT^- by the addition of a small portion of MeOH to a hot solutions led to a plastic material upon cooling. Removing this material from the solution resulted in it setting relatively quickly as a glass. Mechanically pulling the material in its plastic state from its self drew out fine strands, which formed glassy fibres within sec. This glass material by ^{1}H NMR showed that the ratio of the complex MBA^+@Q[7] D-HT^- was maintained at a ratio of 1 : 1 : 1 for each component. Analysis by ORD showed no enantio-selection. In contrast, a hot water solution of the racemic mixture of MBA^+@Q[7]L-HT^- with a small portion of MeOH added promoted crystallisation upon cooling. Crystallisation by this approach was reproducible and facile. However, these crystals also showed no enantio-selection and again the composition was maintained at a ratio of 1 : 1 : 1.

MBA^+ HT^- combinations, in methanol is known to be an effective method for the separation of R- and S- MBA through repetitive crystallisation.[25] When MBA is encapsulated in Q[7] the separation of its enantiomers becomes ineffective.

3. Conclusion

It has been found that the Q[7] induces a significant chiroptic effect shown both in ORD and CD spectra. The two examples presented, which have similar binding constants, show different effects, which is likely to be as a consequence of the binding orientations of the encapsulated chiral ammonium ion in combination with the tartrate counterion. It has been shown that the chiral anion HT^- has an association role as part of the supramolecular structure leading to additional chiroptic effects. The close association of HT^- to a Q[7] cavity-bound achiral ammonium ion was demonstrated by CD spectra as well as significant changes to CD and ORD spectra of different enantiomer combinations of the complex ABC^+@Q[7]HT^-. The chiral HT^- was clearly able to imprint an influence upon the complex enabling a selectivity toward a significant ee as much as ~33 % for ABC^+. However, in the case of MBA^+@Q[7]HT^- neither enantiopure forms of HT^- were effective. A possible explanation for this negative result may relate to the depth of encapsulation within the cavity of the chiral CH–NH_3^+ group, as the magnitude of the upfield shift of these proton resonances were significantly different $\Delta\delta$ 0.33 and 0.08 ppm for MBA^+ and ABC^+ respectively.

While crystallisation may not be the best approach to achieving enantiopure ammonium ions with the aid of Q[7] the partial success in achieving selectivity suggests alternative

techniques such as chromatography could be applicable. In addition, tartrate may not be an ideal choice and an alternative chiral auxiliary anion with a greater propensity to crystallisation may improve the outcome.

ABC^+@Q[7]HT^- proved amenable to enantio-selectivity but was also interesting from two other perspectives. The back-folding of the two rings enabling complete accommodation within the Q[7] cavity; and the relative orientation of the two rings leading to complementary twists or the beginnings of a helical structure.

MBA^+@Q[7]HT^- was also significant in the formation of a material of glass in the supramolecular combination of MBA^+@Q[7]D-HT^- as opposed to the ready crystallisation of MBA^+@Q[7]L-HT^- indicating a packing arrangement dictated by the chirality of at least the anion in spite of its inability to influence enantio-selectivity in crystallisation.

4. Experimental Section

4.1 General

^{1}H NMR spectra were recorded at 400 MHz at 25 °C unless otherwise stated. Spectra were referenced to 4.78 ppm using the residual ^{1}H signal of D_2O. 1D spectra were recorded with between 16 and 64 transients. With water suppression and a saturation time of 1 s, NOESY spectra were acquired using 2048 data points in t2 (with a spectral width of 4200 Hz) for 400 t1 values with a pulse repetition rate of 1.5 s with 16–128 scans per fid. Mixing times of 400 ms were used.

All sample solutions were prepared in high purity water. Sonication was used to assist in dissolution of Q[7] where necessary. All solutions for ORD were at a concentration of 2 mM. ORD were recorded on a polarimeter at $\lambda = 546$ and 436 nm at 20 °C using a microcell of 10 cm length and a volume of 1 cm^3. CD spectra were recorded on a CD spectrometer in the wavelength range of 205–250 nm at 20 °C using a rectangular quartz cell (path length 1 mm) and all solutions were at a concentration of 1.5 mM.

Chemicals used benzylamine, (R)-α-methyl benzylamine, (S)-α-methyl benzylamine, (R,R)-1-amino-2-benzyloxycyclopentane, (S,S)-1-amino-2-benzyloxycyclopentane, D-tartaric acid and L-tartaric acid were all obtained from commercial sources and used without purification. Cucurbit[7]uril was prepared according to our previously reported procedure.[26]

Hydrochloride salts were prepared by the addition of 32 % HCl (0.1 mL) to the relevant amine (1 mmol). The excess acid was removed *in vacuo* and the remaining salts were left to dry in a desiccator.

The tartrate salts were prepared as solutions (H_2O or D_2O depending on the application) in mole ratios of 1 : 1 of the relevant tartaric acid added to the relevant amine and these solutions were made up to a volume suitable to give concentrations specified above.

Each of the chiral starting amines and the tartrates were individually verified by ORD and CD, and were found to have exact mirror spectra for each enantiomeric pair.

4.2 ORD Study

Q[7] was added as a solid repeatedly to the salt solutions in accurate increments of ~0.1–0.2 mole equiv. At each addition solutions were thoroughly mixed and sonicated to facilitate the dissolution of Q[7]. Generally 8 additions were carried out for each analysis.

4.3 CD Study

Each combination of chiral amine/Q[7]/tartaric acid were prepared in water or D_2O in ratios of 1 : 1 : 1 respectively. The ratios were verified by ^{1}H NMR, following preparation as concentrated D_2O samples ~35 mM and diluting with H_2O to 1.5 mM solution for analysis. Samples prepared directly in H_2O gave indistinguishable results by CD.

4.4 Crystallisation of Racemic Q[7] Complexes

Racemic MBA was used to prepare the complexes MBA^+@Q[7] D-HT^- and MBA^+ @Q[7] L-HT^-. These complexes were prepared in high purity water and concentrated with warming then extended periods of cooling in a repetitive process. No crystals were obtained for MBA^+@Q[7] D-HT^- only a very viscous plastic layer at the bottom. Repeating the process with small additions of MeOH while hot gave, after a cooling period, a similar plastic material. Removing this material and leaving it in the air gave a glass. The ^{1}H NMR spectrum of the glass was identical to MBA^+@Q[7] D-HT^- 1 : 1 : 1 (SI). The ORD showed no enantio-selectivity. The complex MBA^+@Q[7] L-HT^- under similar conditions crystallised readily to give colourless crystals. The ORD in this case also showed no enantio-selectivity however, the ratio of each component was also 1 : 1 : 1.

Racemic ABC was used to prepare the complexes ABC^+@Q[7] D-HT^- and ABC^+@Q[7] L-HT^-. These complexes were prepared in high purity water and concentrated with warming then extended periods of cooling in a repetitive process until crystallisation occurred. By ^{1}H NMR these crystals were identical to the spectra of ABC^+@Q[7] D-HT^- or ABC^+@Q[7] L-HT^- with component ratios of 1 : 1 : 1 (SI). The molar rotations were measured before and after the guest was displaced with adamantly ammonium chloride (solid ~1 equiv), which resulted in an increase, as would be expected for the free ABC^+ (see Figure 4). The molar rotation was determined using Figure 4a, this was consistent with enantio-selectivity for S-ABC^+ L-HT^- and R-ABC^+ D-HT^- [θ] 80 and −200 deg $dmol^{-1}$ cm^2, calculating for 12 and 33 % ee respectively.

Supporting Information Available: Additional ORD and CD spectra are available. Details of the determination of binding constants through curve fitting of ORD titration data or ^{1}H NMR titration data is also available. ^{1}H NMR spectra of each ammonium guest encapsulated in Q[7] has been provided together with the NOESY spectrum of R-ABC$^+$@Q[7] D-HT$^-$.

Acknowledgements

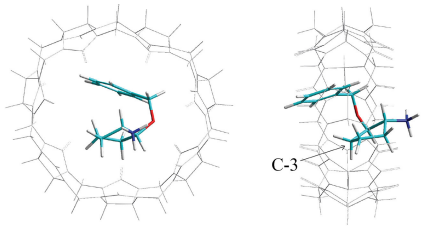
This work was supported by the UNSW Canberra, Postgraduate Student Research Scholarship program.

References

[1] S. Lee, *Chiral Drug Separation, Encyclopedia of Chemical Processing* DOI: 10.1081/E-ECHP-120039232, Taylor and Francis, 449–458, **2006**.
[2] J. Martens, R. Bhushan, *Hel. Chim. Acta* **2014**, *97*, 161–187.
[3] A. Thayer, *Chem. Eng. News* **2005**, *83*, 49–53.
[4] S. Mane, *Anal. Methods,* **2016**, *8*, 7567–7586.
[5] Y. Wang, A. M. Chen, *Org. Process Res. Dev.*, **2008**, *12*, 282–290.
[6] E. Pálovics, F. Faigl, E. Fogassy, (2012) *Advances in Crystallization Processes; Separation of the Mixtures of Chiral Compounds by Crystallization,* Y. Mastai (Ed.), InTech, DOI: 10.5772/2672 www.intechopen.com.
[7] V. Schurig, R. *Glaser, Special Issue: Chiral Separation, Isr. J. Chem.* **2016**, *56*, 886–1090.
[8] Y. Zhang, S. Yao, H. Zeng, H. Song, *Curr. Pharm. Anal.* **2010**, *6*, 114–130.
[9] W. J. Xu, J. H. Hong, H.-K. Han, J. S. Kang, W. Lee, *Bull. Korean Chem. Soc.* **2011**, *32*, 2493–2496.
[10] B. J. V. Verkuijl, J. G. De Vries, B. L. Feringa, *Chirality* **2011**, *23*, 34–43.
[11] J. P. Smuts, X.-Q. Hao, Z. Han, C. Parpia, M. J. Krische, D. W. Armstrong, *Anal. Chem.* **2014**, *86*, 1282–1290.
[12] R. Nishioka, S. Harada, *J. Chromatogr.* **2016**, *37*, 65–71.
[13] V. Mandadapu, A. I. Day, A. Ghanem, *Chirality* **2014**, *26*, 712–723.
[14] L. Yuan, R. Wang, D. H. Macartney, *Tetrahedron: Asymmetr.* **2007**, *18*, 483–487.
[15] N. F. Ghazali, D. A. Patterson, A. G. Livingston *Chem Comm.* **2004**, 962–963.
[16] Modelling was performed with HyperChem 8.0.10 where the ABC$^+$ molecule was back-folded manually consistent with the NOESY correlations then placed in an optimised Q[7] cavity and minimised in molecular mechanics MM+ which maintained a back-folded state.
[17] W. S. Jeon, K. Moon, S. H. Park, H. Chun, Y. H. Ko, J. Y. Lee, E. S. Lee, S. Samal, N. Selvapalam, M. V. Rekharsky, V. Sindelar, D. Sobransingh, Y. Inoue, A. E. Kaifer, K. Kim, *J. Amer. Chem. Soc.* **2005**, *127*, 12984–12989.
[18] O. Buyukcakir, F. T. Yasar, O. A. Bozdemir, B. Icli, E. U. Akkaya, *Org. Lett.* **2013**, *15*, 1012–1015.
[19] V. Sindelar, S. Silvi, A. E. Kaifer, *Chem. Commun.* **2006**, *20*, 2185–2187.
[20] A. E. Kaifer, W. Li, S. Silvi, V. Sindelar, *Chem. Commun.* **2012**, *48*, 6693–6695.
[21] L. Lei, L. Luo, X.-L. Wu, G.-H. Liao, L.-Z. Wu, C.-H. Tung, *Tetrahedron Lett.* **2008**, *49*, 1502–1505.
[22] H.-J. Buschmann, L. Mutihac, E. Schollmeyer, *J. Incl. Phenom. Macrocycl.* **2006**, *56*, 363–368.
[23] V. Kolman, P. Kulhanek, V. Sindelar, *Chem. Asian J.* **2010**, *5*, 2386–2392.
[24] A. Urbach, V. Ramalingam, *Isr. J. Chem.* **2011**, *51*, 664–678.
[25] A. Ault, *Org. Synth.* **1969**, *49*, 93.
[26] A. I. Day, A. P. Arnold, R. J. Blanch, B. Snushall, *J. Org. Chem.* **2001**, *66*, 8094–8100.

Received: September 26, 2017
Accepted: December 21, 2017
Published online on ■■, ■■■

FULL PAPER



*W. Wu, M. P. Cronin, L. Wallace, A. I. Day**

1 – 9

An Exploration of Induced Supramolecular Chirality Through Association of Chiral Ammonium Ions and Tartrates with the Achiral Host Cucurbit[7]uril