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Chiroptic behaviour of a chiral guest in an achiral cucurbit[7]uril host

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Abstract—The protonated forms of the chiral molecules (*S*)- and (*R*)-*N*-benzyl-1-(1-naphthyl)ethylamine ($BNEAH^+$) form very stable 1:1 guest–host complexes with cucurbit[7]uril in aqueous solution. The stoichiometry and stability constants for the guest–host complexes were determined by ^1H NMR, UV–visible and circular dichroism spectroscopy and electrospray mass spectrometry. The molecular optical rotations of the guests increase in magnitude by about 5-fold upon formation of the $\{BNEAH{\cdot}CB[7]\}^+$ species. Energy minimized structures of the guests and guest–host complexes indicate changes in the dihedral angles about the stereogenic centre upon ion-dipole and H-bonding interactions between the ammonium hydrogens of the guest and the carbonyl groups of the cucurbituril portals. The increases in the optical rotations are discussed in terms of restricted rotations of the naphthyl groups and in preferential solvation of benzylamine in the cucurbit[7]uril cavity.

1. Introduction

Cucurbit[*n*]urils (CB[*n*]) are a family of cyclic host molecules comprised of glycoluril units linked by a pair of methylene groups, possessing fairly rigid hydrophobic cavities of low polarizability,[1–4] which can be accessed through carbonyl lined portals. The CB[6] host, first prepared over a century ago,[5] was rediscovered in 1981 by Mock et al.,[6] and numerous aspects of its host–guest chemistry have been investigated over the next two decades.[1] More recently, the methods for the syntheses of the other CB[*n*] cogeners ($n = 5$, 7, 8 and 10)[7] and some substituted derivatives have improved significantly and there has been considerable interest in the properties of these host molecules during the past five years.[4] In particular, CB[7], with its superior solubility in aqueous solution, has been shown to exhibit remarkable stability in its inclusion complexes. As with β-cyclodextrin,[8] the cavity of CB[7] can accommodate aromatic molecules, with a portal diameter of 5.4 Å and an internal cavity diameter of 7.3 Å.[4] A variety of hydrophobic cationic guest molecules,[9–12] such as viologens,[10] metallocene cations (with $K_{CD} > 10^{12}\ M^{-1}$),[13] have been examined with CB[7]. The CB[7] has been used to modify the chemical and spectroscopic properties of guests molecules.[1–4] This has included photodimerization reactions,[14] stabilizations of dyes and other guest molecules,[15] and fluorescence switches.[16]

The formations of supramolecular guest–host complexes involving chiral components have been widely investigated.[17] Chiral selectivity in guest–host molecular recognition has been employed in chiral separations and asymmetric synthesis and catalysis. Achiral host molecules which are induced-fit type receptors, such as crown ethers,[18] calixarenes and resorcarenes,[19] and porphyrin tweezers,[20] have formed chiral host–guest complexes by including chiral guests. Amongst the chiral cyclic host molecules available, the cyclodextrins have perhaps received the greatest attention.[21] Unlike the chiral cyclodextrin host molecules, the cyclic cucurbituril hosts are achiral, and as such should not exhibit any chiral selectivity in guest–host molecular recognition. Rekharsky et al.,[22] however, have recently shown that enantiomeric host–guest complexes composed of CB[6] with (*R*)- or (*S*)-2-methylpiperazine provide 95% enantioselectivity towards binding of a second chiral guest, (*S*)-2-methylbutylamine. Herein we report on the chiroptic behaviour of the guest–host complexes composed of the optical isomers of protonated *N*-benzyl-1-(1-naphthyl)ethylamine ($BNEAH^+$) in an achiral cucurbit[7]uril host cavity (Scheme 1).

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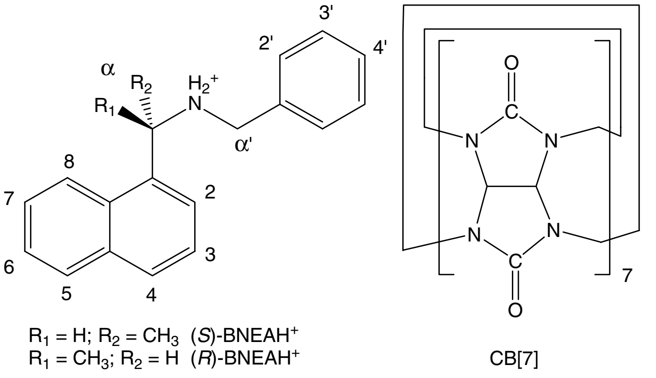

Scheme 1. The structures of the guests (*S*)- and (*R*)-BNEAH$^+$ and the host cucurbit[7]uril.

2. Results and discussion

2.1. Host–guest complexes

The conjugate acids of the chiral molecules (*S*)- and (*R*)-*N*-benzyl-1-(1-naphthyl)ethylamine (BNEAH$^+$) form very stable 1:1 guest–host complexes with cucurbit[7]uril in aqueous solution. A Job's plot of the absorbance changes at 305 nm in mixtures of (*R*)-BNEAH$^+$ with CB[7] has a maximum at $[\mathrm{CB[7]}]/[\mathrm{CB[7]}] + [\mathrm{BNEAH}^+] = 0.50$, indicative of a 1:1 host–guest complex. This is supported by the electrospray mass spectral peak at $m/z = 1425.5$ for the $\{\mathrm{BNEAH{\cdot}CB[7]}\}^+$ species. The BNEAH$^+$ guest molecules are potentially able to be included in the cavity of the cucurbit[7]uril via the hydrophobic naphthyl and/or the benzyl groups. The guest molecules also possess an amine group which, when protonated, forms attractive ion-dipole and H-bonding interactions with the carbonyl groups in the portals of CB[7].

By observing the changes in the ^{1}H NMR spectrum of the BNEAH$^+$ cations upon addition of CB[7], the stoichiometry of the guest–host complex and the portion of the guest which may be included within the CB[7] cavity, may be determined. Inclusion of the guest results in the appearance of new resonances for the bound guest and the disappearance of the free guest peaks. This is indicative of the exchange between the free and bound guest at a rate which is slow on the NMR timescale, as observed for some other cationic aromatic guests in CB[7]. Upfield shifts in the guest protons are observed for the hydrogens which reside within the hydrophobic deshielding CB[7] cavity. Downfield shifts in the proton resonances have been associated with hydrogens in the vicinity of the shielding carbonyl groups of the CB[7] portals, while little change is expected in the resonances for hydrogens completely outside of the host cavity (see Fig. 1).

Examination of the ^{1}H NMR spectra as a function of the $[\mathrm{CB[7]}]/[\mathrm{BNEAH}^+]$ ratio revealed that the upfield shifts occur for the aromatic and methylene resonances associated with the benzyl group, while the resonances for the majority of the aromatic naphthyl protons do not shift. The exception is for the naphthyl H7 and H8 protons, which experience a modest downfield shift, consistent with their proximity to the carbonyl groups on one of the CB[7] portals.

The energy-minimized gas-phase structures of the guest and guest–host complexes were determined. These results indicated that CB[7] has a considerable preference for the

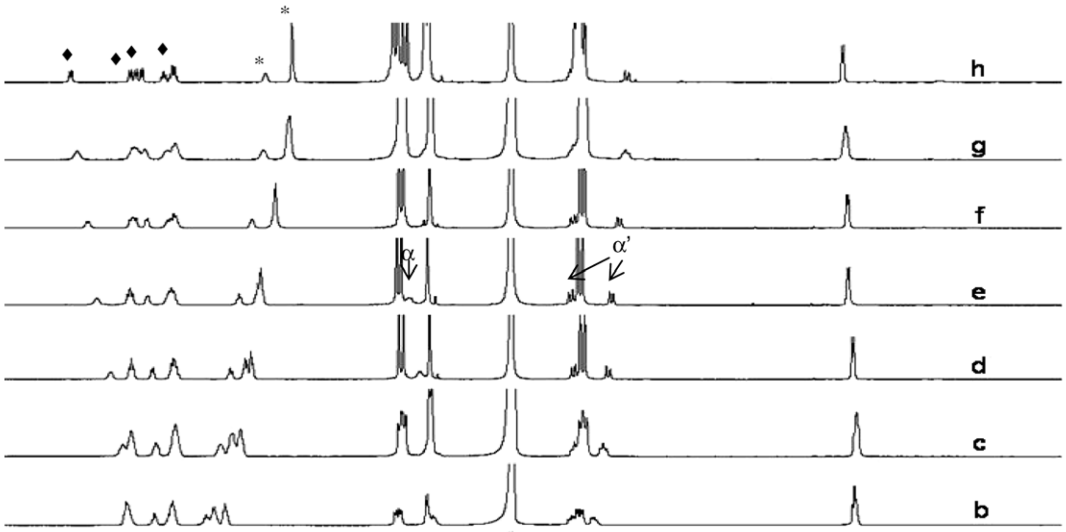

Figure 1. ^{1}H NMR spectra of the (*R*)-BNEAH$^+$ in the (a) absence and (b–h) presence of CB[7] in D_2O. The ratios of $[\mathrm{CB[7]}]/[(R)\text{-}\mathrm{BNEAH}^+]$ are (b) 0.17, (c) 0.33, (d) 0.50, (e) 0.66, (f) 0.85, (g) 1.05 and (h) 2.01. The symbols (∗) and (◆) are for the aromatic phenyl and naphthyl protons, respectively. The α- and α′-protons are adjacent to the naphthyl and phenyl rings, respectively.

benzyl rather than the ethylnaphthyl portion of the guest molecules. In addition, the binding of a CB[7] to the benzyl group sterically inhibits the binding of a second CB[7] over the naphthyl rings.

The guest–host stability constant for the $\{BNEA{\cdot}CB[7]\}^+$ complex is too large to measure by conventional titrations using UV–visible or ^{1}H NMR spectroscopy. Instead, the stability constant was determined by a ^{1}H NMR competition method[9] using 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid ($K_{CB[7]} = (1.82 \pm 0.22) \times 10^7$ M^{-1})[9] as the competing guest. Employing a limiting quantity of CB[7], a stability constant of $K_{CB[7]} = (1.05 \pm 0.13) \times 10^8$ M^{-1} was calculated from the relative integrations of the free and bound competing guests. This stability constant is in the range of binding constant, $K_{CB[7]} = 10^4$–10^{12} M^{-1}, observed for protonated amine or diamine guests with hydrophobic aliphatic or aromatic cores.[9–12] The magnitude of the binding constant is quite dependent on the size and shape of the guest molecule bearing the amine group. Stability constants of similar magnitude have been reported for other inclusion complexes of CB[7] with aromatic guests, such as protonated 2-aminoanthracene ($K_{CB[7]} = 8 \times 10^5$ M^{-1}),[16] α,α′-diamino-*p*-xylene ($K_{CB[7]} = 1.84 \times 10^9$ M^{-1}),[9] and 1,4-bis(4,5-dihydro-1*H*-imidazol-2-yl)benzene ($K_{CB[7]} = 5.2 \times 10^9$ M^{-1}).[12]

2.2. Effect of inclusion on chiroptic behaviour

The inclusion of the enantiomers of the *N*-benzyl-1-(1-naphthyl)ethylammonium cation (BNEAH$^+$) in CB[7] results in considerable increases in the magnitudes of their optical rotations (Fig. 2). The molar optical rotation for the *R* isomer increases from −208 for the free guest to −940 deg cm^2 dmol^{-1} for the guest–host complex, while a corresponding change from +208 to +940 deg cm^2 dmol^{-1} was observed for the *S* isomer.

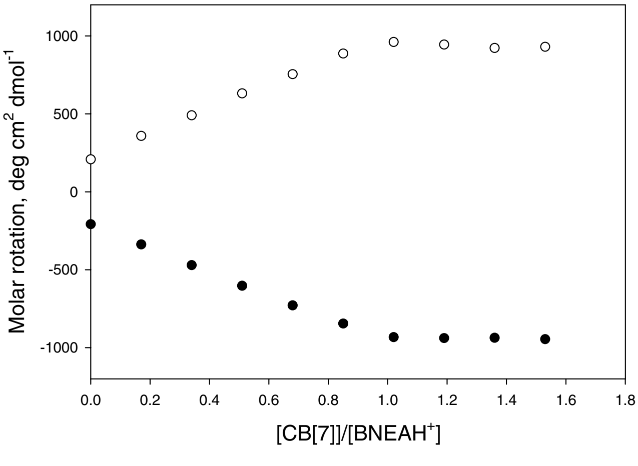

Figure 2. The dependence of the molar optical rotation $[M]_D$ on the ratio of [CB[7]]/[BNEAH$^+$] in aqueous solution at 25 °C for (*S*)-BNEAH$^+$ (○) and (*R*)-BNEAH$^+$ (●). [BNEAH$^+$] = 2.5 mM.

The changes in the optical rotation are most likely a combination of conformational[23] and solvational[24] effects. The gas-phase energy-minimized structures (Fig. 3) indicate a 75–80° change in the torsional angles between the C*–CH$_3$ or C–NH$_2$$^+$ bonds and the plane of the naphthyl ring upon binding of (*S*)-BNEAH$^+$ to CB[7], while the torsion angles between the C*–CH$_3$ or C*–C1 bonds and the NH$_2$$^+$–CH$_2$ bond change by 25–30° for the (*R*)-isomer. While there is free rotation of the naphthyl ring in the free guest, it is clearly restricted in its rotation with respect to the chiral centre by virtue of the cucurbit[7]uril binding of the benzyl portion of the guests. Although the protonated (*R*)- and (*S*)-α-methylbenzylammonium cations bind strongly to CB[7], there is no observed change in their optical rotations upon complexation to the host molecule.

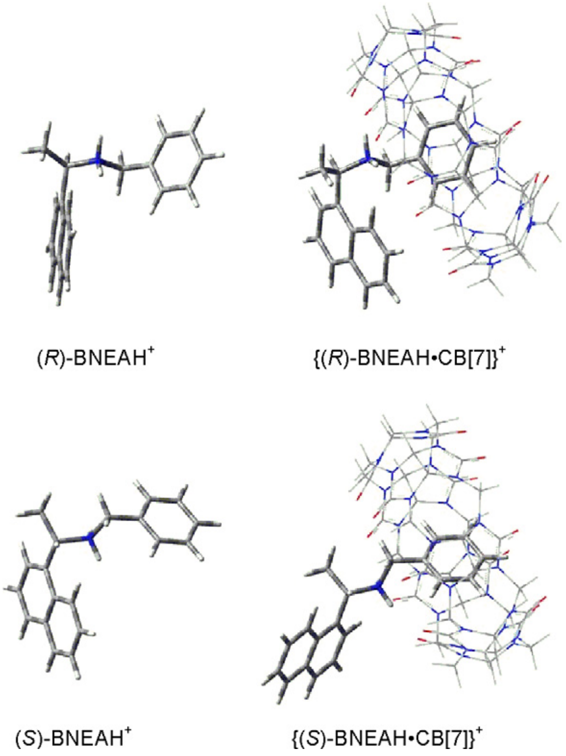

Figure 3. The energy-minimized gas-phase structures for (*R*)- and (*S*)-BNEAH$^+$ guests and the 1:1 host–guest complexes with CB[7].

The circular dichroism spectra of the BNEAH$^+$ isomers and their CB[7] host–guest complexes were determined in aqueous solution (Fig. 4). The main features in these mirror image spectra are peaks in the 225–230 nm and 275–285 nm regions, which correspond to the ^1B_b and ^1L_a transitions, respectively. For the [BNEAH]$^+$ isomers, the two peaks are of opposite signs, with the (*R*)-isomer negative and the (*S*)-isomer positive for the 225–230 nm peak and the opposite for the 275–285 nm.

Upon inclusion in the CB[7], the CD spectra exhibit a decrease in the magnitude of the peak at 225–230 nm, with a slight hypsochromic shift. There is a reversal of the sign and an increase in the magnitude of the 275–285 nm peak, which exhibits a bathochromic shift. The inclusion of the benzyl group in the CB[7] cavity thus changes the circular

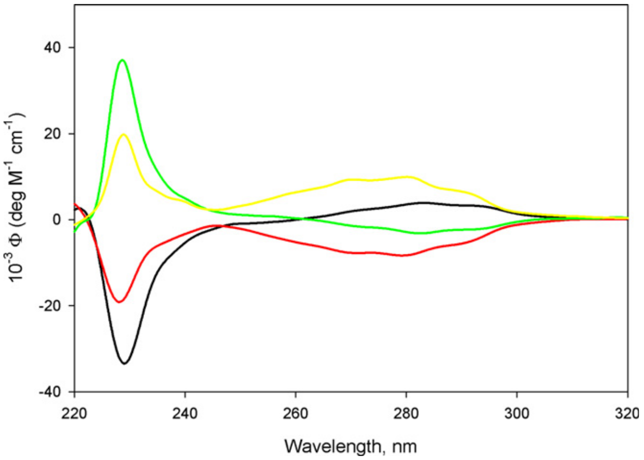

Figure 4. Circular dichroism spectra for (*R*)-BNEAH$^+$ (black), {(*R*)-BNEAH]·CB[7]}$^+$ (red), (*S*)-[BNEAH$^+$ (green), and (*S*)-BNEAH·CB[7]}$^+$ (yellow). The concentrations of BNEAH$^+$ and CB[7] are 0.10 and 0.15 mM, respectively, in aqueous solution.

dichroic behaviour of the naphthalene ring. Further studies with other chiral naphthalene and aromatic guest compounds are underway to better understand the chiroptic behaviour of chiral guests in this achiral host molecule.

3. Conclusions

In conclusion, the use of specific ion-dipole and H-bonding interactions between a chiral guest and an achiral host molecule can have a profound effect on the optical rotations of the optical isomers through complexation induced geometric changes. This study has shown that by restricting the rotation of the naphthyl chromophore in a chiral guest through inclusion of the benzyl portion in the cavity of cucurbit[7]uril, the optical rotation is increased and changes are observed in the CD spectrum. We are currently expanding this study to determine if other chiral amine guests, such as cinchonine and quinine, exhibit similar chiroptic behaviour.

4. Experimental

4.1. Materials

The hydrochloride salts of (*R*)- and (*S*)-*N*-benzyl-1-(1-naphthyl)ethylamine were used as received from Aldrich. Cucurbit[7]uril was prepared by a literature method.[7b]

4.2. Methods

4.2.1. Spectroscopy. The UV–visible spectra were recorded on a Hewlett-Packard 8452A spectrometer. The ^{1}H NMR spectra were measured using a Bruker AV-400 spectrometer in D_2O, using the residual HDO signal as an internal reference. The optical rotation data were obtained on AUTOPOL V polarimeter with $\lambda = 589$ nm at $T = 25.3$ °C. Samples were prepared in acidic aqueous solution 10 cm cells. The circular dichroism spectra were recorded using a Jasco J-715 spectrometer at room temperature with a cell of 1.0 cm pathlength. The concentrations of (*R*)/(*S*)-BNEAH$^+$ and CB[7] were 0.10 and 0.15 mM, respectively in aqueous solution.

4.2.2. Inclusion stability constant. The stability constant for the {(*R*)-BNEAH·CB[7]}$^+$ guest–host complex was determined by means of a ^{1}H NMR guest competition experiment[9] using sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 (TMSP, $K_{\text{CB[7]}} = (1.82 \pm 0.22) \times 10^7$ M^{-1} s^{-1})[9] as the competing guest. A deficiency of CB[7] (0.516 mM) was used compared to the concentrations of (*R*)-BNEAH$^+$ (3.36 mM) and TMSP (1.68 mM).

4.2.3. Energy-minimization calculations. The structures of the BNEAH$^+$ cations and the {BNEAH·CB[7]}$^+$ guest–host complexes were computed by energy minimizations using GAUSSIAN 03, Revision C.02 programs[25] run on the computing facilities of the High Performance Virtual Computing Laboratory (HPVCL) at Queen's University. The structure of the complex was originally constructed using ChemDraw and Chem 3D (ChemOffice 7.0, CambridgeSoft) programs and imported into GAUSSIAN 03. The basis set used for the calculations was HF/3-21G**.

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