A Chiral Pybox Ligand as a New Chiral Shift Reagent for Secondary Dialkylammonium Cations

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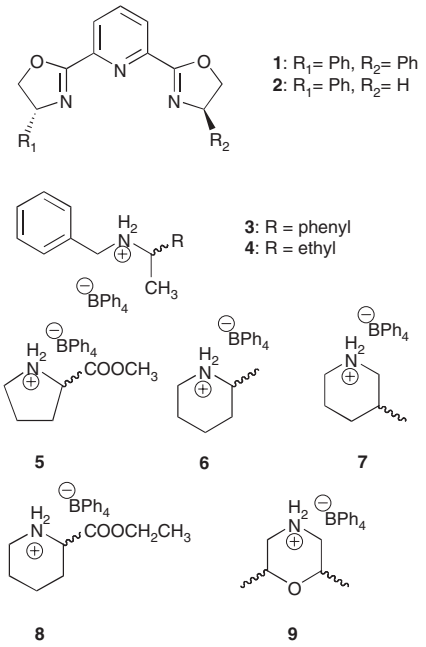
A new chiral shift reagent, a C_2 chiral phenylpybox ligand, targeted for secondary dialkylammonium cations has been exploited.

Chiral recognition of primary and secondary ammonium cations has received much attention toward efficient separation processes in pharmaceutical industries, because they are often found in the molecular structures of biologically active compounds, such as GABA, dopamine, methylphenidate, and ACE inhibitors. Design of chiral host compounds toward chiral ammonium cations dated back to early 1970s.[1] Cram and co-workers first demonstrated that enantiomeric 1,1′-binaphthyl crown ethers recognize selectively one enantiomer from the racemic mixture.[1] Since then, a large number of chiral macrocyclic compounds have been reported to exhibit chiral recognition of various ammonium cations.[2,3] Most of them have been focused on primary alkylammonium cations by charge–dipole interactions and hydrogen bonds between the crown ethers and the cations.[3] Some other types of host compounds such as Kemp's acid derivatives,[4] linear monosaccharides,[5] and tripodal oxazolines[6] have been recently reported. However, less attention has been ever paid to those of secondary dialkylammonium cations, because the complex formations require threading of the alkyl groups of the ammonium cations into the macrocyclic rings[7] and this situation makes it difficult to design the effective host compounds. In this report, we present a new chiral host compound which functions as a chiral shift reagent targeted for secondary dialkylammonium cations.



Our molecular design for the secondary dialkylammonium cations laid on complementary hydrogen bonding between a pybox (2,6-bis(4,5-dihydrooxazol-2-yl)pyridine, **1**) ligand and two positively charged hydrogen atoms of the secondary dialkylammonium cations. We recently reported that they form 1:1 complexes by X-ray crystallography and ^{1}H NMR titration.[8] X-ray structural analysis revealed that a cleft between the two oxazoline rings acts as a binding pocket for them. Introduction of the substituent groups as steric barriers provides C_2 chiral environments around the binding site. Indeed, a wide range of the chiral pybox ligands have been already prepared for asymmetric catalytic reactions.[7] This prompted us to investigate chiral recognition of C_2 chiral pybox ligand (2,6-bis(4,5-dihydro-4-phenyloxazol-2-yl)pyridine, **2**). In this report, we report utility of **2** as a chiral shift reagent for various secondary dialkylammonium and chiral discrimination of **2**.

NMR titrations of **2** with various dialkylammonium tetraphenylborates were carried out by mixing the salts with 1–3 equiv. of **2** in $CDCl_3$ or $CDCl_3$–CD_3CN (600 MHz, 1:4 = *v*:*v*, 25 °C). Addition of **2** into a solution of (*RS*)-**3** induced the large separation of the resonances as shown in Figure 1. For example, the doublet signal (1.263 ppm) of 1-methyl protons in (*RS*)-**3** moved to two doublet signals at 1.127 and 1.449 ppm in the presence of **2**. The quartet methine proton of the guest was split to two sets, and the triplet signal of β-methyl groups was also to two sets. They showed enough separations for estimation of the enanitiomeric excess. In order to assign the resonances, we investigated formation of the complexes with optically active (*R*)-**3** and (*S*)-**3**. The methyl resonance of (*R*)-**3** was shifted to upfield and that of (*S*)-**3** was downfield, and they could be assigned

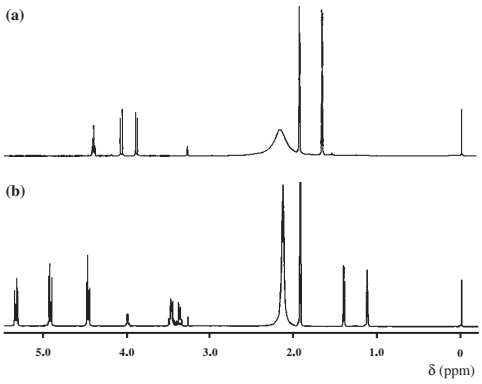


Figure 1. ^{1}H NMR spectra of (a) (*RS*)-**3**, and (b) (*RS*)-**3** in the presence of an equimolar amount of **2** in $CDCl_3$–CD_3CN =1:4 (*v*:*v*).

to those of the racemic **3**. Therefore, the methyl group of (*R*)-**3** and (*S*)-**3** should exist under the different magnetic environments due to shielding or deshielding of the two phenyl groups of the host **2**. Relative slow exchange between them enables to separate the signals. This is supported by broadening of the resonance of the benzyl protons in the guest induced by addition of **2** due to the suppressed mobility of the protons near the ammonium nitrogen atom.

In order to demonstrate scope and limitation of **2** as the chiral shift reagent, we investigated the chemical shift changes in the various racemic secondary dialkylammonium cations (**4**–**9**). Table 1 summarizes separated signals of the ammonium cations induced by **2**. In a series of benzyl alkylammonium cations as guests, the substituents groups attached to the asymmetric center were split into two resonances by addition of one or more equivalents of **2**. Substituted piperidiniums also gave efficient splits by formation of the diastereomeric complexes. Especially, although **7**, **8**, and **9** have the asymmetric carbons at β-positions, they gave the similar splitting pattern in their signals. These results indicate that the host **2** acts as the useful chiral shift reagent for a wide range of secondary dialkylammonium cations.

Table 1. Chemical shift changes ($\Delta\delta$) of the proton resonances of the guest ammonium cations induced by **2**

Salts	$\Delta\delta$/ ppm	Salts	$\Delta\delta$/ ppm
3[a]	0.53	**7**[c]	0.17
4[b]	0.16	**8**[a]	0.12
5[a]	0.22	**9**	0.18
6[a]	0.28		

[a]The methine resonance of the asymmetric carbon, [b]1-methyl resonance, and [c]3-methyl resonance.

In order to evaluate the abilities of chiral discrimination, we investigated binding constants of the complexes with optically active ammonium cations by ^{1}H NMR titration (600 MHz, in $CDCl_3$–CD_3CN 1:4 = *v*:*v*, 25 °C). The methyl resonances of (*R*)-**3** and (*S*)-**3** were shifted to upfield and downfield by additions of **2** and were saturated nearly at 1:1 host–guest ratio, as shown in Figure 2. The non-linear curve fitting provides the association constants $K_R = (4.4 \pm 2.0) \times 10^3$ (mol dm^{-3}) for (*R*)-**3**, and $K_S = (6.7 \pm 0.6) \times 10^3$ (mol dm^{-3}) for (*S*)-**3**, respectively. In the case of **5**, the binding constants for (*R*)-**5** and (*S*)-**5** were calculated to $K_R = (2.8 \pm 0.3) \times 10^3$ (mol dm^{-3}) and $K_S = (1.8 \pm 0.5) \times 10^3$ (mol dm^{-3}), respectively. In all cases, the complexes have the relatively high binding constants enough to form the 1:1 complexes at the 1:1 molar ratio under the ordinary conditions (1 mmol dm^{-3}). However, the phenyl groups of **2** are not so bulky as to discriminate chirality of the secondary dialkylammonium cations. The ratios of the association constants (K_R/K_S) are 0.66 and 1.6 for **3** and **5**, respectively. This indicates that the host **2** shows the relative low chiral discrimination abilitiy. The magnitudes are similar to those of primary alkylammonium cations with chiral crown ethers,[3] Kemp's acid derivatives[4] and linear monosaccharides host compounds.[5] The low selectivity and the reversed affinity observed for the configurational isomers between **3** and **5** are ascribed to small difference in steric hindrance around the binding sites. The π–π interactions between the host and the guest affect the guest affinity. The induced chemical shift changes of the dialkylammonium cations are attributed to the chiral environment of the C_2 chirality of **2** by deshielding and shielding difference in the phenyl groups.

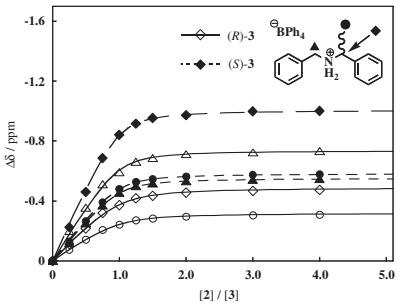


Figure 2. Chemical shift changes of the methine (rectangle), benzyl (diamond) and 1-methyl (circle) protons of (*R*)-**3** (open) and (*S*)-**3** (filled) by addition of **2** in $CDCl_3$–CD_3CN =1:4 (*v*:*v*).

In conclusion, we demonstrated that the C_2 chiral pybox ligand works as the effective chiral shift reagent for various secondary dialkylammonium cations. In contrast to the presence of several good chiral shift reagents for primary ammonium guests, that for secondary ammonium guests has so far been limited.[3–6] The wide variation of the substituent groups of the bisoxazoline ligands established in the present system is important and would provide designable chiral host compounds for the specific secondary dialkylammonium cations.

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