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A convenient synthesis of chiral dioxocyclens and application as chiral solvating agents

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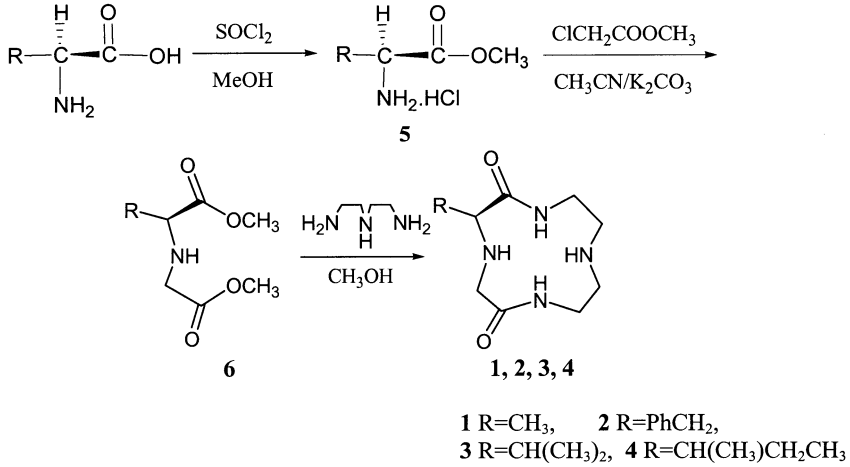
Abstract—This paper reports a very short and efficient synthesis of chiral dioxocyclens starting from natural amino acids. NMR experiments were undertaken to assess the chiral recognition properties of these chiral macrocycles. The NMR spectra of mandelic acid or its derivatives in the presence and absence of the chiral dioxocyclens showed that these macrocycles have different enantiomeric discriminating ability. It was revealed that this type of dioxocyclen may be promising hosts for chiral discrimination.

Chiral macrocyclic compounds have been recognized as successful and promising chiral selectors for molecular recognition mainly because of their inherent reduced flexibility and complexation ability.[1] Macrocyclic amides that bear the dual features of macrocyclic polyamines and oligopeptides, can act as both hydrogen bond acceptors and donors and can form complexes with neutral molecules. So this kind of chiral dioxocyclen may have potential applications for enantiomeric recognition, especially with neutral molecules and anions, such as drugs and biomolecules.[2] However, the preparation of these molecules is often fraught with difficult procedures, low yields and laborious purifications. Only a few reports about the synthesis and application of chiral peraza-macrocycles have appeared.[3] Thus, the development of an efficient synthesis of these highly desirable chiral compounds remains of key interest. In this paper we report a very short and efficient synthesis of chiral dioxocyclens (Scheme 1) and their application as chiral solvating agents (CSAs) for enantiomeric discrimination.



Scheme 1. The synthesis of dioxocyclens starting from amino acids.

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L-Amino acids were converted into methyl esters, and reacted with methyl chloroacetate to give the intermediates **6**, which then reacted with diethylenetriamine to afford the desired chiral products after recrystallization twice from CH_3CN. The total yields were about 10%. The structures were confirmed by MS, ^1H, ^{13}C NMR spectra and microanalysis.[4]

This synthetic approach has some advantages in that all the products were synthesized without *N*-protection and high dilution conditions are not required. The introduction of a chiral unit into a macrocyclic ring is expected to give steric rigidity at the chiral carbon that may be helpful in chiral recognition, and different substituents at the chiral center will provide information on the mechanism of the chiral recognition. Furthermore, the imido NH can be functionalized easily.[5]

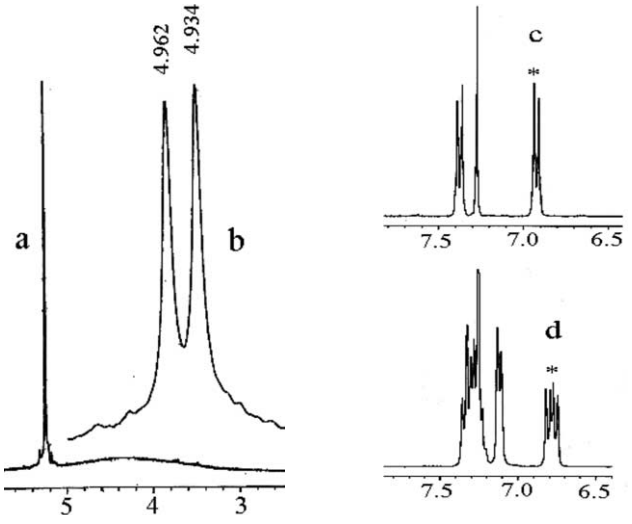


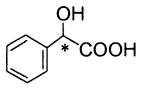
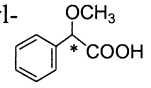
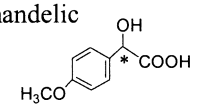
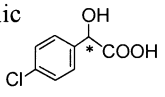
Figure 1. (a) The methine proton signal of mandelic acid; (b) the methine proton signals of mandelic acid in the presence of an equimolar amount of compound **2**; (c) part of phenyl proton signal of 4-methoxymandelic acid; (d) part of phenyl proton signal of 4-methoxymandelic acid in the presence of an equimolar amount of compound **2**.

Many approaches are available for studying the structure and dynamics of multimolecular complexes. The NMR method is perhaps most often used for the examination of such complexes in solution because it can provide direct structural and dynamic information.[6] Studies on the molecular recognition were carried out on a 300 MHz NMR spectrometer using the compounds **1**–**4** as CSAs.

The racemates of mandelic acid and its derivatives were chosen as substrates. The signal of the methine hydrogen for these substrates is a sharp singlet and does not overlap with the peaks of the other proton signals in their ^1H NMR spectra. Therefore, it is an ideal probe for discrimination. Samples for analysis were prepared by mixing equimolar amounts of the substrate and the chiral dioxocyclen (the concentrations were normally 20 mM) in $CDCl_3$.

The methine proton signals of all substrates were shifted upfield about 0.1 ppm in the presence of the chiral dioxocyclen. Some were split into two peaks due to the different interactions of the two enantiomers of the substrate with the CSA. This confirmed that chiral recognition had occurred. Fig. 1 (a and b) shows the methine signal in the ^1H NMR spectra of mandelic acid in the absence and presence of an equimolar amount of the compound **2**. The non-equivalence ($\Delta\Delta\delta$, Hz) is the difference of the chemical shifts of corresponding protons of the two enantiomers in the presence of the CSA. In Fig. 1b, the methine signal has clearly split into two peaks ($\Delta\Delta\delta$ 8.4 Hz). The methine signal of the (*R*)-enantiomer is more intense than that of the (*S*)-enantiomer because the (*R*)-mandelic acid was added in slight excess to the solution. The fact that the (*R*)-enantiomer has larger chemical shift changes than the (*S*)-enantiomer reveals that the (*R*)-mandelic acid has a stronger interaction with compound **2**. Table 1 summarizes the $\Delta\Delta\delta$ values of the methine signals of the enantiomers of the four substrates in the presence of the dioxocyclens **1**∼**4**, respectively. It can be seen that

Table 1. Differences ($\Delta\Delta\delta$) between the chemical shifts of the methine signals of the enantiomers of the substrates in the presence of the dioxocyclens **1**–**4** (host:guest = 1:1)

Substrates	ΔΔδ (Hz)			
	1	**2**	**3**	**4**
mandelic acid 	1.2	8.4	2.1	3.0
α-methoxyphenyl-acetic acid 	–	8.2	3.9	–
4-methoxymandelic acid 	–	7.2	–	–
4-chloromandelic acid 	–	7.5	–	1.8

dioxocyclens **1**∼**4** exhibit different enantiomeric discriminating ability. In particular, for recognition of mandelic acid, less steric hindrance at the chiral carbon of the dioxocyclen leads to weaker chiral recognition. As for compound **1**, although the proton signals of the substrates shifted over 0.1 ppm, little chiral recognition occurred.

The chemical shifts of the amide N*H* signals in the ^{1}H NMR spectra of the dioxocyclens move downfield by 0.1–0.3 ppm. Meanwhile, both phenyl ring proton signals of the four substrates and compound **2** were shifted. This implies that a π–π interaction might occur between the phenyl rings of the substrates and that of the host. As to 4-methoxymandelic acid, the peaks of the phenyl ring proton signals which were not overlapping with the host phenyl ring proton signals were clearly split into quartets in the presence of compound **2** (Fig. 1 c and d), and the proton signals of the MeO group also split into two peaks ($\Delta\Delta\delta = 3.6$) because of the change in electronic density on the phenyl ring.

In conclusion, the chiral dioxocyclen **2** is the best CSA for the four substrates we chose. The phenyl group plays an important role in chiral recognition. We have used an efficient and simple synthetic methodology for novel chiral dioxocyclen synthesis and we have introduced this kind of chiral dioxocyclen into molecular recognition research as CSAs. All chiral dioxocyclens are amphiphiles, and they may be further functionalized, providing opportunities for the design and investigation of more effective chiral macrocyclic hosts that may be used for chiral recognition, enantiomeric separation and enzyme models.

Acknowledgements

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4. Compound **1**: $[\alpha]_D^{20} = 23.71$ ($c = 0.8$, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.55$ (br, 1H, CON*H*), 7.38 (br, 1H, CON*H*), 3.17–3.24 (q, $^3J = 6.9$ Hz, 1H, NHC*H*CO), 3.38–3.68 (m, 4H, 2CONHC*H*, NCH_2CO), 2.58–3.11 (m, 6H, 2CONHC*H*·2NHCH_2), 1.83 (br, 2H, 2N*H*), 1.34–1.36 (d, $^3J = 6.6$ Hz, 3H, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.97, 172.03, 62.25, 53.94, 45.34, 45.05, 38.31, 37.63, 20.59; MS (FAB): 215 $[M+1]^+$, mp: 181–183°C. Anal. calcd for $C_9H_{18}N_4O_2$, C 50.45; H, 8.47; N, 26.15. Found: C, 50.6; H, 8.1; N, 25.4%. Compound **2**: $[\alpha]_D^{20} = 40.34$ ($c = 1.0$, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ (br, 1H, CON*H*), 7.49 (br, 1H, CON*H*), 7.26–7.42 (m, 5H, Ph), 3.27–3.64 (m, 5H, 2CONHC*H*, NHCH_2CO, NHC*H*CO), 3.03–3.22 (m, 2H, 2CONHC*H*H), 2.64–3.01 (m, 6H, 2NHCH_2, PhCH_2), 1.94 (br, 2H, 2N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.69, 172.01, 129.32, 129.26, 127.48, 67.49, 57.31, 45.32, 45.04, 39.90, 38.36, 37.63: MS (FAB): 291 $[M+1]^+$, mp: 192–194°C. Anal. calcd for $C_{15}H_{22}N_4O_2$: C, 62.05; H, 7.64; N, 19.30. Found: C, 61.6; H, 7.3; N, 19.3%. Compound **3**: $[\alpha]_D^{20} = 39.11$ ($c = 1.0$, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (br, 1H, CON*H*), 7.30 (br, 1H, CON*H*), 3.04–3.77 (m, 6H, NHCH_2CO, 2CONHCH_2), 2.67–2.99 (m, 5H, NHC*H*CO, 2NHCH_2), 1.86 (br, 2H, 2N*H*), 1.61–2.12 (m, 1H, CH_3CHCH_3), 0.97–1.05 (m, 6H, 2CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.89, 171.86, 72.53, 54.72, 45.69, 45.33, 38.12, 31.72, 19.70, 18.46, MS (FAB): 243 $[M+1]^+$, mp: 201–203°C. Anal. calcd for $C_{11}H_{22}N_4O_2$: C, 54.52; H, 9.15; N, 23.12. Found: C, 53.8; H, 9.2; N, 23.3%. Compound **4**: $[\alpha]_D^{20} = 22.32$ ($c = 1.0$, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.63$ (br, 1H, CON*H*), 7.26 (br, 1H, CON*H*), 2.98–3.71 (m, 6H, NCH_2CO, 2CONHCH_2), 2.60–2.97 (m, 5H, 2NHCH_2, NHC*H*CO), 1.72–1.78 (m, 3H, 2N*H*, CH_2CHCH_3) 1.08–1.60 (m, 2H, $CHCH_2CH_3$), 0.89–0.97 (m, 6H, 2CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.11, 172.14, 71.43, 54.72, 45.45, 45.07, 38.37, 37.91, 37.88, 25.28, 15.91, 11.56: MS (FAB): 257 $[M+1]^+$, mp: 213–215°C. Anal. calcd for $C_{12}H_{24}N_4O_2$: C, 56.22; H, 9.44; N, 21.86. Found: C, 56.0; H, 9.1; N, 21.4%.
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