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Novel rigid chiral macrocyclic dioxopolyamines derived from L-proline as chiral solvating agents for carboxylic acids

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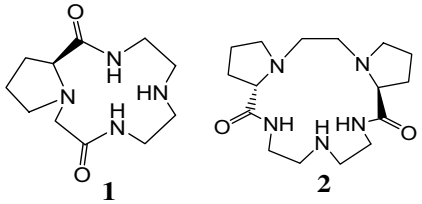
Abstract—^{1}H NMR was employed to investigate the chiral recognition ability of two novel L-proline derived rigid chiral macrocyclic dioxopolyamines, (12*S*)-1,4,7,10-tetraazadicyclo[10.3.0]pentadecane-3,11-dione **1** and (8*S*,18*S*)-1,4,10,13,16-pentaazatricyclo[16.3.0.0^{4,8}]heneicosane-9,17-dione **2**, the latter of which is newly synthesized. The crystal structures of the two macrocyclic compounds were determined by X-ray single crystal structure analysis. The Job plots indicate that compound **1** forms a 1:1 instantaneous complex with (*R*)- or (*S*)-mandelic acid while compound **2** forms a 1:2 instantaneous complex with each of the two guests above. Association constants of compound **1** with (*R*)- and (*S*)-mandelic acids were determined by a nonlinear least-squares fitting method. Both of the macrocycles exhibited good chiral recognition toward the enantiomers of the racemic carboxylic acids we chose. It was shown that the macrocyclic dioxopolyamine of C_2 symmetry had a better enantiomeric discriminating ability than that of C_1 symmetry.

1. Introduction

The study of enantiomeric recognition phenomena is of great value in many fields, such as the resolution of racemic mixtures of technically and biologically relevant compounds; the determination of the enantiomeric composition of relevant chiral compounds; the screening of chiral catalysts, etc. Chiral carboxylic acids are the structure units of many natural products and drug molecules, which are classes of compounds with high economic and scientific potential.[1–4] The growing use of enantiomerically pure chiral carboxylic acids has given rise to the need for the development of fast and accurate methodologies for the determination of the enantiomeric composition of chiral carboxylic acids.[5] The use of chiral solvating agents (CSAs) for ^{1}H NMR spectroscopy is one of the most satisfactory and convenient methods for this, which can rapidly assess the enantiomeric composition of chiral compounds.[6–9] Although a great number of chiral macrocyclic compounds for enantiomeric recognitions have already been reported,[10–26] the macrocycles, which can discriminate between the enantiomers of chiral carboxylic acids have been rarely studied.[27–30] In our previous work, we have synthesized several chiral dioxocyclens derived from natural amino acids and studied their properties as CSAs.[31,32] These chiral dioxocyclens bear steric hindrance at the stereogenic carbon and the dual features of macrocyclic polyamines and oligopeptides,[33] which can act as both hydrogen bond acceptors and donors. When the dioxocyclens interact with chiral carboxylic acids, different interactions of the two enantiomers of the substrate with the chiral host occur. As a result they exhibit certain chiral recognition abilities to several chiral carboxylic acids.

In general, the more rigid the macrocycle molecule, the better the enantiomeric recognition.[10,34] With this in mind, L-proline was chosen as the starting material for the synthesis of new chiral macrocycles. We have already reported the efficient synthesis of macrocyclic dioxopolyamine (12*S*)-1,4,7,10-tetraazadicyclo[10.3.0]-pentadecane-3,11-dione **1**, which possesses a unique and rigid pyrrolidinyl group.[35] In light of the fact that



1 **2**

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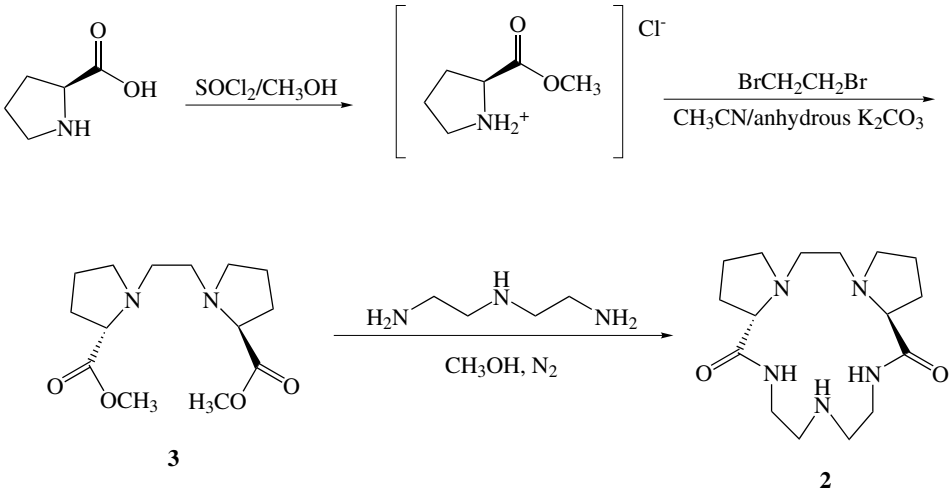


Scheme 1. The synthetic route of compound **2**.

macrocyclic receptors, which possess C_2 symmetry, usually show higher enantioselectivity than those of C_1 symmetry,[10,12] we synthesized another novel L-proline derived rigid chiral macrocyclic dioxopolyamine of C_2 symmetry, (8*S*,18*S*)-1,4,10,13,16-pentaaza-tricyclo-[16.3.0.0^{4,8}]heneicosane-9,17-dione **2** (Scheme 1). The crystal structures of compounds **1** and **2** were determined by X-ray single crystal structure analysis.[36] The abilities of compounds **1** and **2** as CSAs to discriminate several chiral carboxylic acids were also studied. Both of the macrocycles exhibited good chiral recognition toward the enantiomers of the racemic carboxylic acids we chose. It was shown that the macrocyclic dioxopolyamine of C_2 symmetry had a better enantiomeric discriminating ability than that of C_1 symmetry.

2. Results and discussion

The molecular structures of compounds **1** and **2** are shown in Figures 1 and 2. Conventional macrocyclic polyamines have somewhat large conformational flexibilities. In this case, both compounds **1** and **2** have pyrrolidinyl groups, resulting in the enhancement of the structural rigidity, so as to stabilize the macrocyclic conformation. It can be seen that compound **2** of C_2 symmetry has two identical macrocyclic planes, meaning that no matter from which plane the guest interacts with the macrocycle, the enantiomeric discriminating ability remains the same.[10]

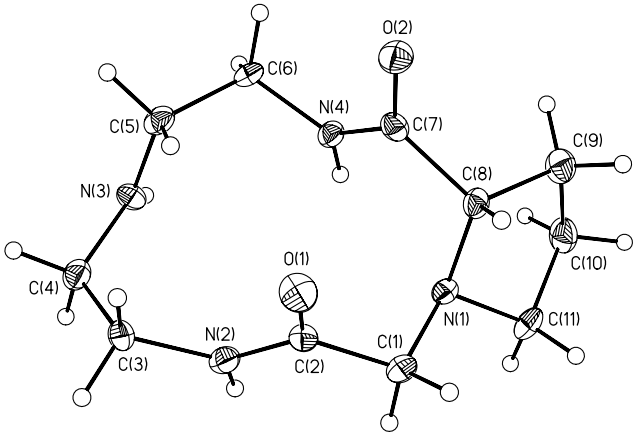


Figure 1. ORTEP drawing of the molecular structure of compound **1** (the molecule of H_2O is omitted for clarity).

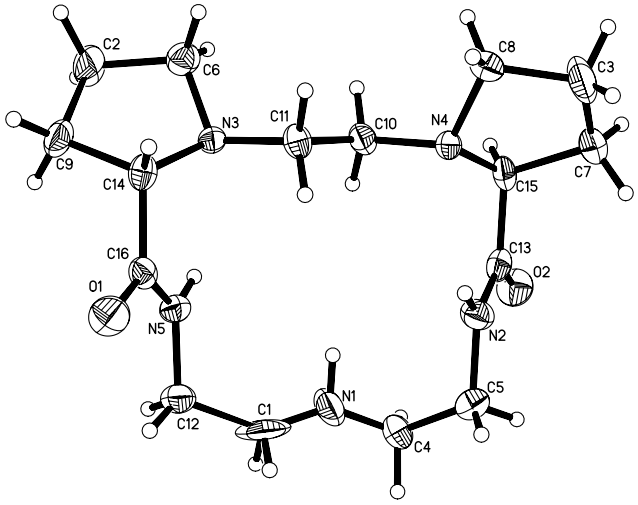


Figure 2. ORTEP drawing of the molecular structure of compound **2**.

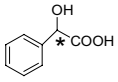
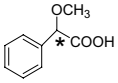
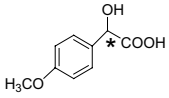
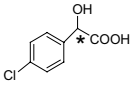
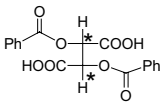
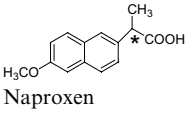
We utilized ^{1}H NMR spectroscopy to investigate the chiral recognition ability of compounds **1** and **2**, while the racemates of mandelic acid and some of its derivatives, dibenzoyltartaric acid and naproxen were chosen as guests. In the presence of compounds **1** and **2**, all the proton signals of the guests were shifted. The $\Delta\delta$ value is the change of chemical shifts. The methine proton signals of mandelic acid and some of its derivatives were shifted upfield by about 0.12–0.32 ppm; the methine proton signals of dibenzoyltartaric acid shifted upfield by 0.33–0.41 ppm, while the methine proton signals of naproxen shifted upfield by only 0.109 and 0.052 ppm. Among all the guest molecules, only naproxen does not possess an oxygen function at the *o*-position of

the carbonyl group. This oxygen function may play a crucial role for a scaffold of hydrogen bonding with NH or N on host molecules. The chemical shift changes mean that the interactions between the CSAs and the guests occurred, while the host–guest complexes formed from the CSAs and the guests, had different complexation induced shifts (CISs). As a whole, the $\Delta\delta$ values for all the guests above were greater in the presence of compound **2** than those in the presence of compound **1**.

It was most important that all the single peaks of the methine protons of all the guests (except naproxen) and those of the α-methoxy group of α-methoxyphenylacetic acid were split into two single peaks in the presence of compounds **1** and **2**, due to the different interactions of the two enantiomers of the guests with the CSA. The nonequivalence ($\Delta\Delta\delta$) is the difference of the chemical shifts of corresponding protons of two enantiomeric guests in the presence of the CSA. From Table 1, it is obvious that compound **2** exhibits a better enantiomeric discriminating ability to the chiral carboxylic acids than compound **1**. This may be due to the larger ring structure and the C_2 symmetry of compound **2**. The largest $\Delta\Delta\delta$ value (18.9 Hz) of the methine proton was observed when dibenzoyltartaric acid served as the guest (Fig. 3). This showed that compound **2** had the best enantiomer discriminating ability to dibenzoyltartaric acid when compared to the other guests we chose. As with naproxen, only 2.4 Hz nonequivalence of the α-methyl appeared in the presence of compound **2** (Fig. 4). From the results of the chiral discrimination in the different molar ratios for compound **2**, it was generally found that a molar ratio of 1:2 for compound **2** with guests resulted in a greater nonequivalence in chemical shift (Table 1).

The ^{1}H NMR spectra of compounds **1** and **2** with (*R*)- and (*S*)-mandelic acids in a variety of ratios in $CDCl_3$ at a constant total concentration of 5.0×10^{-3} M were obtained. It was found that the methine proton signal of (*R*)- and (*S*)-mandelic acids at δ 5.236 underwent an upfield shift when treated with compound **1** or compound **2**. Figures 5 and 6 are Job plots of $\Delta\delta X$ (the product of the chemical shift change and the molar fraction) versus the molar fraction (X) of (*R*)- or (*S*)-mandelic acid in the mixture.[27,37] For compound **1**, a minimum was observed when compound **1** versus (*R*)- or (*S*)-mandelic acid was 1:1 ($X = 0.5$), which indicates that the host forms a 1:1 instantaneous complex with (*R*)- or (*S*)-mandelic acid under these conditions. It is obvious that the chemical shift changes of (*S*)-mandelic acid were greater than those of (*R*)-mandelic acid in the presence of

Table 1. Chemical shift changes ($\Delta\delta$) and nonequivalences ($\Delta\Delta\delta$) of the methine, the α-methoxy and the α-methyl protons in the ^{1}H NMR spectra (300 MHz) of guests in the presence of compounds **1** and **2** in $CDCl_3$ at 25 °C

Guests		$\Delta\delta$ (ppm)			$\Delta\Delta\delta$ (Hz)		
Ratio (CSA:guest)		**1**	**2**		**1**	**2**	
		(1:1)	(1:1)	(1:2)	(1:1)	(1:1)	(1:2)
 Mandelic acid	–CH	−0.181 −0.190	−0.225 −0.257	−0.222 −0.266	2.7	9.6	13.2
 α-Methoxyphenylacetic acid	–CH	−0.119 −0.129	−0.141 −0.166	−0.170 −0.194	3.9	7.5	7.2
	–OCH_3	−0.120	−0.066 −0.098	−0.090 −0.121	—	9.6	9.3
 4-Methoxymandelic acid	–CH	−0.268 −0.288	−0.292 −0.315	−0.287 −0.322	6.0	6.9	10.5
 4-Chloromandelic acid	–CH	−0.269 −0.281	−0.303 −0.325	−0.286 −0.321	3.6	6.6	10.5
 Dibenzoyltartaric acid	–CH	−0.333 −0.377	−0.349 −0.412	[a]	13.2	18.9	[a]
 Naproxen	–CH	−0.109	0.042	−0.052	—	—	—
	–CH_3	−0.068	−0.019 −0.028	−0.026 −0.034	—	2.7	2.4
		−0.068	−0.019 −0.028	−0.026 −0.034	—	2.7	2.4

[a] Determination not possible.

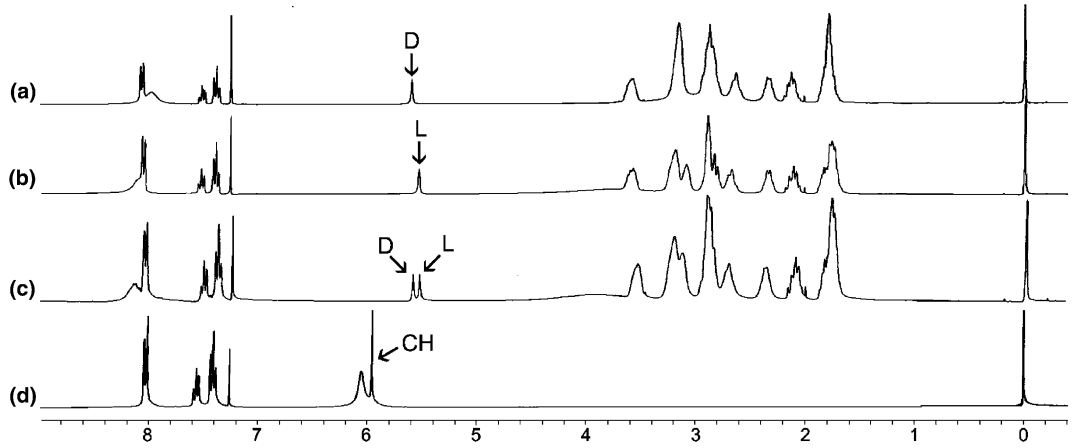


Figure 3. ^{1}H NMR spectra of dibenzoyltartaric acid and equimolar mixtures (10 mM each) of dibenzoyltartaric acid/compound **2**. (a) D-(+)-Dibenzoyltartaric acid and compound **2**; (b) L-(−)-dibenzoyltartaric acid and compound **2**; (c) (±)-dibenzoyltartaric acid and compound **2**; (d) (±)-dibenzoyltartaric acid without compound **2**.

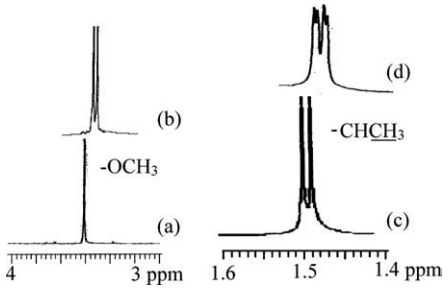


Figure 4. (a) Resonance for the α-methoxy groups of α-methoxyphenylacetic acid; (b) resonance for the α-methoxy groups of α-methoxyphenylacetic acid in the presence of compound **2**; (c) resonance for the α-methyl groups of naproxen; (d) resonance for the α-methyl groups of naproxen in the presence of compound **2**.

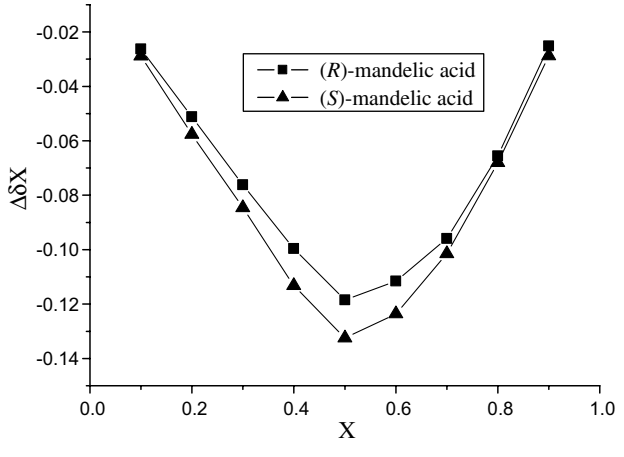


Figure 5. Job plots of compound **1** with (*R*)- and (*S*)-mandelic acids [*X* = molar fraction of the acid, Δδ = chemical shift change of the methine of (*R*)- and (*S*)-mandelic acids].

compound **1**. As with compound **2**, a minimum appeared when compound **2** versus (*R*)- or (*S*)-mandelic acid was 1:2 (*X* = 0.67), indicating that the host formed a 1:2 instantaneous complex with (*R*)- or (*S*)-mandelic acid under the conditions. It can be seen that the chemical shift changes of (*R*)-mandelic acid were greater than those of (*S*)-mandelic acid in the presence of compound **2**.

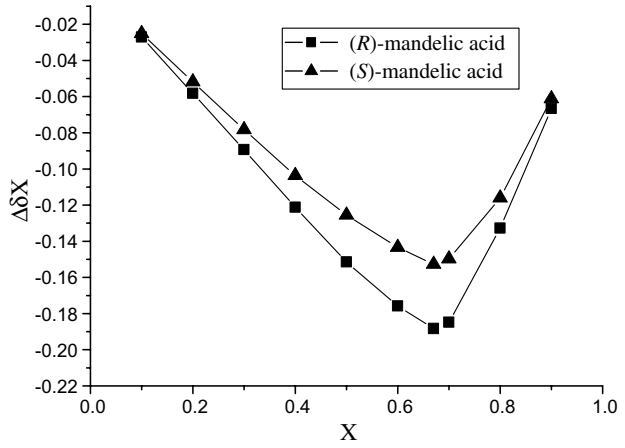


Figure 6. Job plots of compound **2** with (*R*)- and (*S*)-mandelic acids [*X* = molar fraction of the acid, Δδ = chemical shift change of the methine of (*R*)- and (*S*)-mandelic acids].

We also intended to draw the Job plots for dibenzoyltartaric acid with compounds **1** and **2** in $CDCl_3$ (total concentration of 5.0×10^{-3} M, molar fraction of dibenzoyltartaric acid varying from 0.1 to 0.9). The ^{1}H NMR spectra showed that the single peak of the methine protons of the L- and D-forms exhibited a gradual upfield shift with increasing concentration of the guest until the molar fraction equalled to 0.5. When the concentration of the guest sequentially increased, we found that the solution turned turbid ($X \geqslant 0.6$), and white floc appeared in the solution ($X = 0.8$). Hence a molar ratio of host/guest was chosen as 1:1 when dibenzoyltartaric acid was the guest during the discrimination.

In order to assess further the discriminating abilities of compounds **1** and **2**, we made titration curves of compounds **1** and **2** with (*R*)- and (*S*)-mandelic acids (Figs. 7 and 8).[37–40] The conventionally observed target was

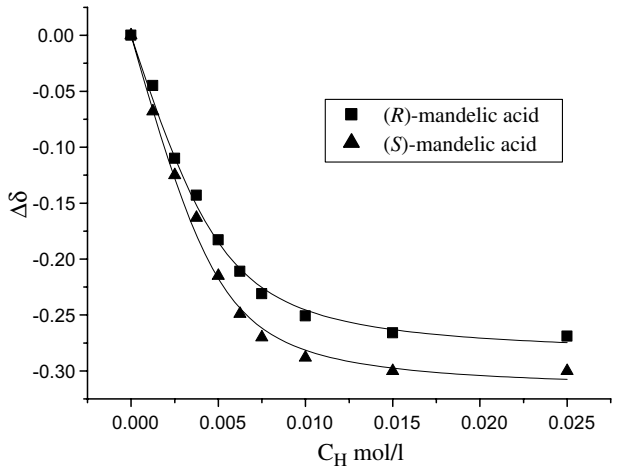


Figure 7. ^{1}H NMR titration curves of compound **1** with (*R*)- and (*S*)-mandelic acids.

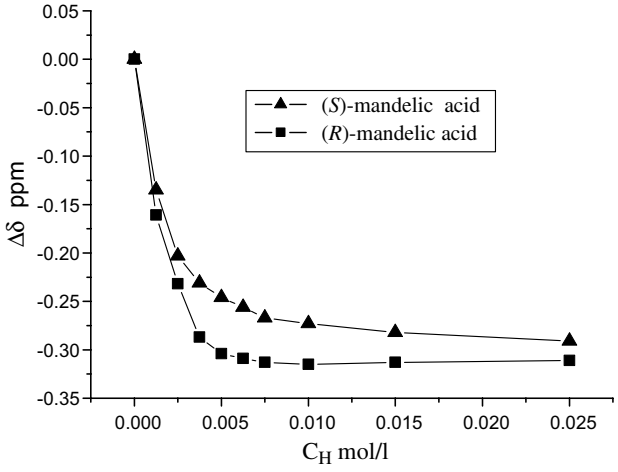


Figure 8. ^{1}H NMR titration curves of compound **2** with (*R*)- and (*S*)-mandelic acids.

the peaks of the protons in the ^{1}H NMR spectra, which were simple, did not overlap with peaks of other protons and had obvious chemical shift changes in the course of the host–guest interaction. The protons of compounds **1** and **2** could not be used as the observed targets because of the complexity of their peaks in ^{1}H NMR spectra. As a result we only chose the methine proton of the guest as the observed target. The association constants of compound **1** with (*R*)- and (*S*)-mandelic acids were determined from the titration curves by a nonlinear least-squares fitting method (Table 2). From Table 2, it was seen that the (*S*)-enantiomer was more strongly bound to compound **1** than the (*R*)-enantiomer. As

Table 2. Association constants K_a of the host–guest complexes of compound **1** with (*R*)- and (*S*)-mandelic acid

	K_a		$K_a(R)/K_a(S)$
	(*R*)-Mandelic acid	(*S*)-Mandelic acid	
Compound **1**[a]	997 ± 17%	1346 ± 18%	0.74

[a] A nonlinear least-squares fitting method.[40]

with compound **2**, which formed 1:2 complexes with (*R*)- or (*S*)-mandelic acid, the titration curves of compound **2** with (*R*)- and (*S*)-mandelic acids were neither in agreement with the nonlinear least-squares fitting method of the 1:1 complex, nor with that of the 1:2 complex of host and guest, which demanded first forming the 1:1 complex, then forming the 1:2 complex over the course of making the titration curve. Hence the association constants of compound **2** with (*R*)- and (*S*)-mandelic acids could not be calculated by a nonlinear least-squares fitting method. From the titration curves of compounds **1** and **2** with (*R*)- and (*S*)-mandelic acids, we found that the chemical shift changes of (*R*)-mandelic acid were always greater than ones of the (*S*)-mandelic acid in the presence of compound **2**. On the contrary, the chemical shift changes of (*S*)-mandelic acid were greater than those of (*R*)-mandelic acid in the presence of compound **1**.

It is known that the solubility of CSAs is crucial to their applied ranges. To find CSAs showing an applicability toward a wide range of substrates remains a challenge.[9] Compounds **1** and **2** are amphiphilic, making it possible for them to be used as the CSA in many solvents, such as methanol, ethanol, acetonitrile, chloroform, ethyl acetate, etc. We mixed equimolar amounts of racemic tartaric acid and compound **2** (the concentrations were normally 10 mM) in CD_3OD at 25 °C, and found that compound **2** also exhibited an enantiomeric discriminating ability to racemic tartaric acid. The $\Delta\Delta\delta$ value of the methine proton was 3.6 Hz.

3. Conclusion

In conclusion, two novel rigid chiral macrocyclic dioxopolyamines derived from L-proline, which have proven to be effective chiral NMR solvating agents for chiral carboxylic acids. In particular, compound **2** with C_2 symmetry has a better enantiomeric discriminating ability than compound **1** with C_1 symmetry, indicating that the symmetry of macrocycle plays an important role in enantiomeric recognition. Compounds **1** and **2** are also amphiphiles and can be used in many solvents, making them possible candidates for further application as the CSAs.

4. Experimental

4.1. General methods

IR spectra were obtained on a Nicolet 170SX FT-IR spectrometer as KBr pellets. NMR spectra were carried out on a Mercury-VX300 spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz). Mass spectra were recorded on a VJ-ZAB-3F-Mass spectrometer using the FAB technique. The elemental analysis was performed on a Carlo-Erba elemental analyzer (Model 1106). Optical rotations were measured with a Perkin–Elmer Model 341LC polarimeter using the sodium D line at 589 nm.

L-Proline was purchased from Chemical Reagents Company, China National Medicines Group. Diethylenetriamine was commercially available and distilled before

use. Reactions were carried out under an atmosphere of dry nitrogen, and the solvents (methanol and acetonitrile) were analytical and thoroughly dried.

4.2. Preparation of (8*S*,18*S*)-1,4,10,13,16-Pentaaza-tricyclo[16.3.0.0^{4,8}]heneicosane-9,17-dione

L-Proline (11.5 g, 0.1 mol) was first converted to the L-proline methyl ester as described.[41] Then 8.65 g (0.046 mol) 1,2-dibromoethane and the L-proline methyl ester were added to a suspension of anhydrous K_2CO_3 (20.7 g, 0.15 mol) in 200 mL CH_3CN and stirred at 50 °C for two days in N_2. The precipitate was filtered off and the filtrate evaporated and then fractionated under reduced pressure to give a pale yellow oil 1,2-bis[(2*S*)-2-carbomethoxy-1-pyrrolidinyl]ethane **3**, bp: 138–140 °C (1 mm); yield 7.18 g (55% based on 1,2-dibromoethane); $[\alpha]_D^{20} = -138.0$ (*c* 4.0, H_2O); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.72$ (s, 6H, 2OC*H*$_3$), 3.14–3.23 (m, 4H, 2NC*H*CO, 2NC*H*H), 2.83–2.87 (m, 2H, 2NC*H*H), 2.57–2.61 (m, 2H, 2NC*H*H), 2.38–2.43 (m, 2H, 2NC*H*H), 2.09–2.14 (m, 2H, 2CH$_2$C*H*HCH$_2$), 1.79–1.97 (m, 6H, 2C*H*$_2$, 2CH$_2$C*H*HCH$_2$).

Intermediate **3** (7.18 g, 0.025 mol) dissolved in 50 mL absolute MeOH was added to a solution of diethylenetriamine (2.57 g, 0.025 mol) in 150 mL absolute MeOH and stirred at 50 °C in nitrogen atmosphere for 10 days. The solvent was then evaporated and the white needle product obtained by recrystallization from CH_3CN. The yield reached was up to 35%. mp: 278–280 °C. $[\alpha]_D^{20} = -234.8$ (*c*, 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (br, 2H, 2CON*H*), 3.60–3.75 (dtd, 2H, $^4J = 3.3$ Hz, $^3J = 7.3$ Hz, $^2J = 14.6$ Hz, 2CH*H*N HCO), 3.13–3.18 (t, 2H, $^3J = 7.2$ Hz, 2NC*H*H), 3.04–3.09 (m, 4H, 2CH*H*NHCO, 2NC*H*CO), 2.79–2.88 (m, 6H, 2NC*H*H, 4NHC*H*H), 2.46–2.56 (m, 2H, 2NC*H*H), 2.13–2.28 (m, 4H, 2NC*H*H, 2C*H*HCH), 1.77–1.86 (m, 7H, 2CH$_2$C*H*$_2$CH$_2$, 2C*H*HCH, CH$_2$N*H*CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.455, 68.678, 55.830, 53.847, 48.612, 38.777, 29.815, 24.395. MS: *m*/*z* 324 ($M^+ + 1$, 100%). Anal. Calcd (%) for $C_{16}H_{29}N_5O_2$: C, 59.42; N, 21.65; H, 9.04. Found (%): C, 59.17; N, 21.78; H, 9.53. IR (KBr): *v* 3292 (m, NH), (2966 (w), 2915 (w), 2855 (w), 2806 (w), CH), 1654 (s, C=O), 1524 (m, C–N).

4.3. NMR shift experiments

NMR shift experiments were performed on a Mercury-VX300 spectrometer at 25 °C. Samples for analysis were prepared by mixing equimolar amounts of compounds **1** and **2** with the guest (the concentrations were normally 10 mM), and by mixing compound **2** (the concentrations were normally 10 mM) and the guest together, with molar ratio of 1:2 for mandelic acid, some of its derivatives and naproxen in $CDCl_3$.

4.4. Evaluation of the stoichiometry of the host–guest complex (Job plots)

The stoichiometry of the host–guest complex was determined according to Job's method of continuous variations. Equimolar amounts of host and guest compound were dissolved in $CDCl_3$. These solutions were distributed among nine NMR tubes in such a way that the molar fractions *X* of host and guest in the resulting solutions increased (or decreased) from 0.1 to 0.9 (and vice versa). The complexation induced shifts were multiplied by *X* and plotted against *X* itself (Job plot).

4.5. NMR host–guest titrations

The guest compound was dissolved in an appropriate amount of solvent and the resulting solution evenly distributed among 10 NMR tubes. The first NMR tube was sealed without any host. The host compound was also dissolved in the appropriate amount of solvent and added in increasing amounts to the NMR tubes, so that solutions with the following relative amounts (equiv) of host versus guest compound (concentration was 5.0×10^{-3} M) were obtained: 0, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 2.00, 3.00, 5.00. K_a was calculated by a non-linear least-squares fitting method for compound **1** from the observed $\Delta\delta$ values and the respective host and guest concentrations.

A representative example is given below: compound **1** versus (*S*)-mandelic acid in $CDCl_3$. Weighed amounts: compound **1**: 30.00 mg in 1 mL; (*S*)-mandelic acid: 4.75 mg in 5 mL. $K_a(S)$ [M^{-1}] = 1346 ± 18%.

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References

1. Coppola, G. M.; Schuster, H. F. *α-Hydroxyl Acids in Enantioselective Synthesis*; VCH: Weinheim, 1997.
2. Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Oxford, 1983.
3. Maier, N. M.; Franco, P.; Lindner, W. *J. Chromatogr. A.* **2001**, *906*, 3–33.
4. Valentine, D., Jr.; Johnsun, K. K.; Priester, W.; Sun, R. C.; Toth, K.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 3698–3703.
5. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.
6. Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.
7. Weisman, G. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, p 153.
8. Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.
9. Iuliano, A.; Uccello-Barretta, G.; Salvadori, P. *Tetrahedron: Asymmetry* **2000**, *11*, 1555–1563.
10. Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313–3361.
11. Still, W. C. *Acc. Chem. Rev.* **1996**, *29*, 155–163.
12. Naemura, K.; Tobe, Y.; Kaneda, T. *Coord. Chem. Rev.* **1996**, *148*, 199–219.
13. Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, *22*, 383–395.

14. You, J.; Yu, X.; Zhang, G.; Xiang, Q.; Lan, J.; Xie, R. *Chem. Commun.* **2001**, 1816–1817.
15. Wenzel, T. J.; Thurston, J. E.; Sek, D. C.; Joly, J.-P. *Tetrahedron: Asymmetry* **2001**, *12*, 1125–1130.
16. Tejeda, A.; Oliva, A. I.; Simón, L.; Grande, M.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **2000**, *41*, 4563–4566.
17. Zhao, H. W.; Hua, W. T. *J. Org. Chem.* **2000**, *65*, 2933–2938.
18. Machida, Y.; Nishi, H.; Nakamura, K. *J. Chromatogr. A* **1998**, *810*, 33–41.
19. Ito, K.; Noike, M.; Kita, A.; Ohda, Y. J. *Org. Chem.* **2002**, *67*, 7519–7522.
20. Chen, G.-M.; Brown, H. C.; Ramachandran, P. V. *J. Org. Chem.* **1999**, *64*, 721–725.
21. Kim, B. M.; So, S. M.; Choi, H. J. *Org. Lett.* **2002**, *4*, 949–952.
22. Tsubakl, K.; Nuruzzaman, M.; Kusumoto, T.; Hayashi, N.; Bin-Gui, W.; Fuji, K. *Org. Lett.* **2001**, *3*, 4071–4073.
23. Zieliński, T.; Achmatowicz, M.; Jurczak, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2053–2059.
24. Bradsaw, J. S.; Thompson, P. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1984**, *21*, 897–901.
25. Naemura, K.; Takeuchi, S.; Hirose, K.; Tobe, Y.; Kaneda, T.; Sakata, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 213–219.
26. Du, C.-P.; You, J.-S.; Yu, X.-Q.; Liu, C.-L.; Lan, J.-B.; Xie, R.-G. *Tetrahedron: Asymmetry* **2003**, *14*, 3651–3656.
27. Lin, J.; Zhang, H.; Pu, L. *Org. Lett.* **2002**, *4*, 3297–3300.
28. Alfonso, I.; Rebolledo, F.; Gotor, V. *Chem. Eur. J.* **2000**, *6*, 3331–3338.
29. Lin, J.; Hu, Q.-S.; Xu, M.-H.; Pu, L. *J. Am. Chem. Soc.* **2002**, *124*, 2088–2089.
30. Xu, M.-H.; Lin, J.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2002**, *124*, 14239–14246.
31. Yuan, Q.; Fu, E.; Wu, X.; Fang, M.-H.; Xue, P.; Wu, C.; Chen, J. *Tetrahedron Lett.* **2002**, *43*, 3935–3937.
32. Yuan, Q.; Xue, P.; Fang, M.-H.; Fu, E.-Q.; Wu, C.-T. *Synth. Commun.* **2003**, *33*, 1911–1916.
33. Kimura, E. *J. Coord. Chem.* **1986**, *15*, 1–28.
34. Still, W. C.; Kilburn, J. D.; Sanderson, P. E. J.; Liu, R.; Wiley, M. R.; Hollinger, F. P.; Hawley, R. C.; Nakajima, M.; Bernardi, A.; Hong, J.-I.; Namgoong, S. K. *Isr. J. Chem.* **1992**, *32*, 41–45.
35. Fang, M.-H.; Fu, E.-Q.; Yuan, Q.; Xue, P.; Wu, C.-T.; Chen, J.-H. *Synth. Commun.* **2002**, *32*, 3629–3635.
36. Crystallographic data for the structures of compounds **1** and **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 228516 and 238240, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data of **1**: $C_{11}H_{20}N_4O_2{\cdot}H_2O$, $M = 258.33$, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 5.1019(8)$ Å, $b = 12.6981(18)$ Å, $c = 20.130(3)$ Å, $V = 1304.1(3)$ Å^3, $D = 1.316$ g/cm^3, $\mu = 0.097$ mm^{-1}, $F(000) = 560$, $Z = 4$, $R_1 = 0.0712$, $\omega R_2 = 0.2518$. Data collection for the crystal structure determination was carried out on an Enraf-Nonius CAD4 diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å) at a temperature of 293 (2)°C. Of the 3304 reflections measured in the $1.90 \leqslant \theta \leqslant 22.98°$ range, 1732 reflections were unique and 1266 reflections with $I > 2\sigma$ (I) were used in structure solution and refinement. $R_{int} = 0.0659$, $w = 1/[\sigma^2(F_o^2) + (0.0379P)^2 + 1.1672P]$, where $P = (F_o^2 + 2F_c^2)/3$. The structure was solved by direct method using SHELX-97. All of the nonhydrogen atoms were refined by full-matrix least-squares methods using anisotropic displacement parameters. Crystal data of **2**: $C_{16}H_{29}N_5O_2$, $M = 323.44$, monoclinic, space group $P2(1)$, $a = 5.2495(10)$ Å, $b = 18.956(4)$ Å, $c = 9.1171(18)$ Å, $\beta = 104.93(3)°$, $V = 876.6(3)$ Å^3, $D = 1.225$ g/cm^3, $\mu = 0.083$ mm^{-1}, $F(000) = 352$, $Z = 2$, $R_1 = 0.099$, $\omega R_2 = 0.2518$. Data collection for the crystal structure determination was carried out on a R-AXIS-IV diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å) at a temperature of 291 (2)°C. Of the 2305 reflections measured in the $2.15 \leqslant \theta \leqslant 23.50°$ range, 2170 reflections were unique while 1501 reflections with $I > 2\sigma$ (I) were used in structure solution and refinement. $R_{int} = 0.1094$. $w = 1/[\sigma^2(F_o^2) + (0.1744P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$. The structure was solved by direct methods using SHELX-97. All of the nonhydrogen atoms were refined by full-matrix least-squares methods using anisotropic displacement parameters.
37. Fielding, L. *Tetrahedron* **2000**, *56*, 6151–6170.
38. Herm, M.; Molt, O.; Schrader, T. *Chem. Eur. J.* **2002**, *8*, 1485–1499.
39. Hirose, T.; Naito, K.; Shitara, H.; Nohira, H.; Baldwin, B. W. *Tetrahedron: Asymmetry* **2001**, *12*, 375–380.
40. Macomber, R. S. *J. Chem. Ed.* **1992**, *69*, 375–378.
41. Elliott, R. L.; Kopecka, H.; Lin, N.-H.; He, Y.; Garvey, D. S. *Synthesis* **1995**, 772–774.