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Enantioselective Recognition for Carboxylic Acids by Novel Chiral Macrocyclic Polyamides Derived from L-/D-tartaric Acid

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The enantioselectivity of chiral macrocyclic polyamides 1–3 derived from L-/D-tartaric acid was investigated by using ^{1}H NMR. All the macrocycles exhibited certain chiral recognition towards the enantiomers of the racemic carboxylic acids we had chosen. As a chiral solvating agent, the compound 3 has the excellent enantiomeric discriminating ability for mandelic acids and its derivatives, containing an α-OH at the chiral carbon, while the compound 2 has the best enantioselectivity towards dibenzoyltartaric acid. The molar ratio and the association constants of the compound 3 with each of the enantiomers of some guest molecules were determined by using the Job's plots and a nonlinear leastsquares fitting method, respectively. The effect of the structure of the hosts or guests on the enantioselectivity of the compound 1–3 has been explored.

Keywords: Macrocyclic polyamides; Chiral recognition; Association constant; Carboxylic acids

INTRODUCTION

In order to facilitate the discovery of new catalysts for asymmetric catalytic reactions and the resolution of the racemic chiral compounds, the researchers are still working hard to develop new methods to rapidly measure how much of each enantiomer is originally in the mixture [1–6], although chiral HPLC is an important analytical technique for stereochemical analysis in the pharmaceutical industry [7–10]. Among all the methods, the use of chiral solvating agents (CSAs) [11–14] for ^{1}H NMR spectroscopy is one of the most satisfactory and convenient methods, which can rapidly assess the enantiomeric composition of chiral compounds without the need of separating enantiomers. Another advantage is that it can provide with direct structural and dynamic information [15–17], which are helpful for the studies on the molecular recognition.

In our previous papers, we have reported the synthesis of several chiral macrocyclic dioxopolyamines derived from L-amino acids and the results of these compounds as CSAs for enantiomeric discrimination towards chiral carboxylic acids [18–21]. Chiral carboxylic acids were chosen as the guest molecules because they are the structural units of many natural products and drug molecules, which are classes of the compounds with high economic and scientific potential [22–26]. Only a few efficient CSAs can be used for the chiral carboxylic acids till now [19,21,27–30]. The chiral macrocycles we synthesized bear steric hindrance at the chiral carbon and the dual features of macrocyclic polyamines and oligopeptides [31], and thus act as both hydrogen bond acceptors and donors. When the macrocycles were used as CSAs, different interactions of the two enantiomers of the chiral carboxylic acids with the chiral hosts occurred. As the results they exhibited certain chiral recognition abilities towards several chiral carboxylic acids. The results revealed that more steric hindrance at the chiral carbon could lead better enantioselectivity of chiral macrocycles and the presence of aromatic groups on the macrocycle would enhance chiral recognition ability [32]. It was also found that the macrocycle with C_2-symmetry had better enantiomeric discrimination than that with C_1-symmetry [21,32]. Comparing with existing CSAs, a practical advantage of the chiral macrocycles we synthesized is that they are

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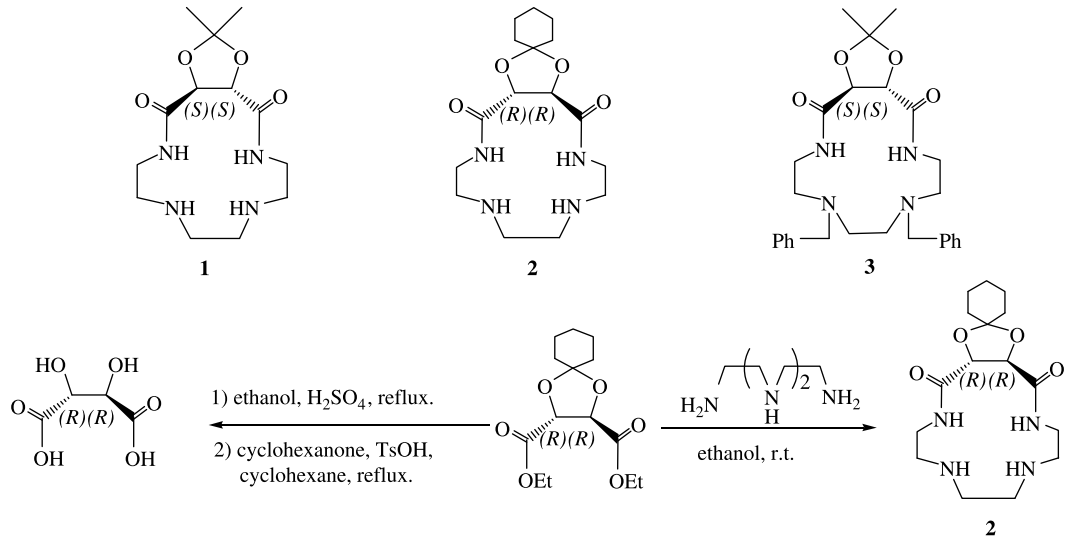


SCHEME 1 The synthetic route of compound **2** and the structures of compounds **1**, **2** and **3**.

amphiphilic and can be used in many solvents, such as methanol, ethanol, acetonitrile, chloroform, ethyl acetate, etc., making them possible candidates for further application.

Recently we have reported the synthesis of some novel chiral macrocyclic polyamides derived from the facile L-/D-tartaric acid with C_2-symmetry [33]. The use of L-/D-tartaric acid as building blocks allows for the convenient introduction of two chiral units into the macrocyclic polyamides. The imines of the macrocycles and the two hydroxyl groups of L-/D-tartaric acid could be modified easily, providing different structural characteristics to the macrocycles and will be helpful to investigate the relationship between the structure and the recognition ability of the macrocycles. In this paper, we would like to present the results by using some of these new chiral macrocycles as CSAs for enantiomeric discrimination towards chiral carboxylic acids. The structures of three chiral hosts and the synthetic route for the compound **2**, which was newly synthesized, are shown in Scheme 1. The crystal structures of compound **3** were determined by X-ray single crystal structure analysis (Fig. 1) [34]. These macrocycles were chosen to undertake the desired chiral recognition for the following reasons. Firstly we would like to investigate how to vary the enantioselectivity of these macrocycles with different rigidity and steric hindrance at the chiral centers of them. Secondly we expect that the magnetic anisotropy of two benzyl groups in the compound **3** will increase the chemical non-equivalence of the proton signal of guest molecules. The following is the results of this investigation and discussion.

RESULTS AND DISCUSSION

^{1}H NMR spectroscopy was used to investigate the chiral recognition ability of the compounds **1**–**3**, while the racemates of mandelic acid and some of its derivatives as well as dibenzoyltartaric acid were chosen as the guests. The signal of the methine hydrogen of these guests is a sharp singlet and does not overlap with the peaks of the other proton signals in their ^{1}H NMR spectra. Therefore, it is an ideal

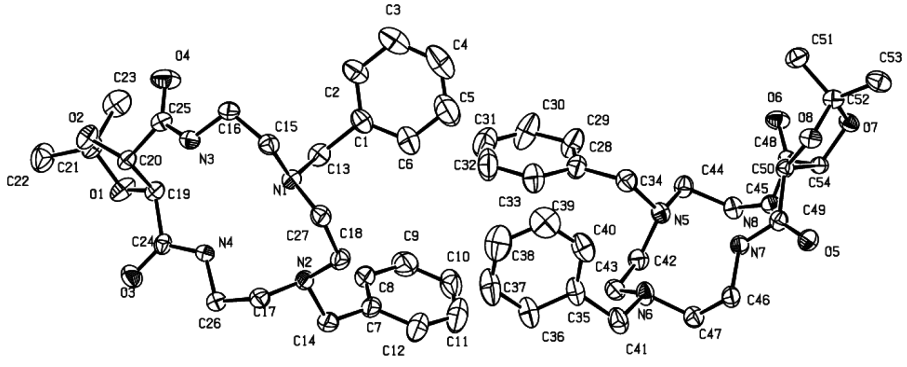
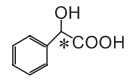
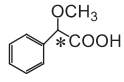
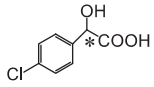
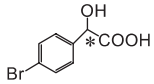
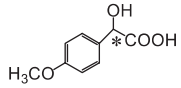
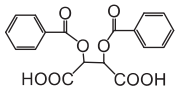


FIGURE 1 ORTEP drawing of the molecular structure of compound **3**.

TABLE I Chemical shift changes (Δδ) and nonequivalences (ΔΔδ) of the methine proton in the ^{1}H NMR spectra (300 MHz) of guests in the presence of compounds **1**, **2** and **3** in $CDCl_3$ at 25°C

Guests	methane	Δδ(ppm)(1:1)			ΔΔδ (Hz)		
		1	2	3	1	2	3
 mandelic acid	–CH	− 0.316 − 0.335	− 0.291 − 0.307	− 0.211 − 0.245	5.7	4.8	10.2
 α-methoxy-phenylacetic acid	–CH	− 0.171 − 0.194	− 0.200 − 0.217	− 0.053 − 0.066	6.9	5.1	3.9
 4-chloro-mandelic acid	–CH	− 0.312 − 0.324	− 0.337 − 0.349	− 0.219 − 0.251	3.6	3.6	9.6
 4-bromo-mandelic acid	–CH	− 0.338 − 0.351	− 0.315 − 0.330	− 0.222 − 0.263	3.9	4.5	12.3
 4-methoxymandelic acid	–CH	− 0.307 − 0.327	− 0.322 − 0.337	− 0.190 − 0.225	6.0	4.5	10.5
 dibenzoyltartaric acid	–CH	− 0.478 − 0.503	− 0.473 − 0.525	− 0.196 − 0.227	7.5	15.6	9.3

probe for discrimination. The samples for analysis were prepared by mixing equimolar amounts of the guest and the chiral macrocycle (the concentrations were normally 20 mM) in $CDCl_3$.

In the presence of each of the compounds **1**–**3**, the signal of the methine proton of all these guests was upfield shifted. And meanwhile a downfield chemical shift of the proton signal of the amido bond in the compounds **1**–**3** had occurred. The chemical shift changes meant that there were interactions between the CSAs and the guests, namely the host–guest instantaneous complexes had been formed. The Δδ value is the change of chemical shifts. In the presence of the compound **1** or **2**, the Δδ values of the methine proton signals of all guests were 0.17–0.52 ppm, while in the presence of the compound **3**, the Δδ values were only 0.04–0.26 ppm. The phenomenon may be caused by the presence of two benzyl groups in compound **3**. The increased steric barriers on the macrocyclic molecules may weaken the interactions between the CSAs and the guests, and meanwhile the methine proton of guests may locate in the deshielding field of the aromatic rings of compound **3**.

The most important phenomenon was that the methine proton signals of all guests were split into two peaks due to the formation of two instantaneous diastereotopic complexes between the CSAs and the enantiomers of the guests, respectively. This confirmed that chiral recognition had occurred. The nonequivalence (ΔΔδ) is the difference of the chemical shifts of corresponding protons of two

FIGURE 2 (a) The methine proton signal of 4-bromo-mandelic acid; (b) the methine proton signals of 4-bromo- mandelic acid in the presence of an equimolar amount of compound **3**.

enantiomers of the guests in the presence of the CSAs [19,21]. The greater the value of the nonequivalence (ΔΔδ), the better the chiral recognition ability of the CSAs. The value of the nonequivalence (ΔΔδ) depends on the stability of two instantaneous diastereotopic complexes and the chemical environment of the probe groups of the guests in above instantaneous complexes.

Table I collects the chemical shift changes (Δδ) and nonequivalences (ΔΔδ) of the methine proton of all guests in the ^{1}H NMR spectra in the presence of compounds **1**, **2** or **3**, respectively. From Table I, we found that all the three compounds had shown good chiral recognition ability towards the enantiomers of the racemic carboxylic acids we had chosen. Among compound **1**–**3**, the compound **3** exhibited the greatest ΔΔδ value towards mandelic acids and its derivatives, containing an α-OH at the chiral carbon and thus had the best chiral discriminating ability towards these guests. The results may be ascribed to two aspects; On one hand, the magnetic anisotropy of the benzyl groups in the compound **3** may increase the chemical non-equivalence of the methine proton signal, on the another hand, the α-OH of the guests may be an important group for the interactions between the compound **3** and the guest molecules. Figure 2 showed the corresponding methine signal in the ^{1}H NMR spectra of the racemic 4-bromo-mandelic acid in the absence and presence of an equimolar amount of the compound **3**. The ΔΔδ value of the two enantiomers of the racemic 4-bromo-mandelic acids had reached 12.3 Hz.

According to the Table I, we further found that the compounds **1** and **2** had shown much better chiral recognition ability to dibenzoyltartaric acid than to mandelic acid and its derivatives. In the case of the compound **2**, the largest ΔΔδ value (15.6 Hz) of the methine proton of racemic dibenzoyltartaric acid was obtained, namely the compound **2** had the best enantioselectivity to dibenzoyltartaric acid among the three hosts (Fig. 3). It means that the compounds **1** and **2**, which have less steric hindrance than compound **3**, more suitably fit dibenzoyltartaric acid and the presence of another –COOH in the guest has also enhanced the interactions between the CSAs and the guest. The best enantioselectivity of the compound **2** towards dibenzoyltartaric acid may benefit from the spirane structure fixed on the chiral centers of the compound **2**.

A series of ^{1}H NMR spectra were obtained by using different ratios of compound **3** with (*R*)-and (*S*)-mandelic acid (or (D)-and (L)-dibenzoyltartaric acid) in $CDCl_3$ at a constant total concentration of 3.0×10^{-3} M. We plotted the Job's plots [35,36], that is the curves of the product (ΔδX) of the chemical shift change (Δδ) and the molar fraction (X) versus the molar fraction (X) of optical pure guest in the mixture, for determining the stoichiometric ratio of host and guest in the complex [37,38].

Figure 4 shows the Job's plot of (*R*)-/(*S*)-mandelic acid with compound **3**. A minimum ΔδX was observed when the molar ratio of the compound **3** and (*R*)- or (*S*)-mandelic acid was 1:1 (X = 0.5), which indicated that host **3** and (*R*)- or (*S*)-mandelic acid formed a 1:1 instantaneous complex. Obviously, the chemical shift changes of (*S*)-mandelic acid were

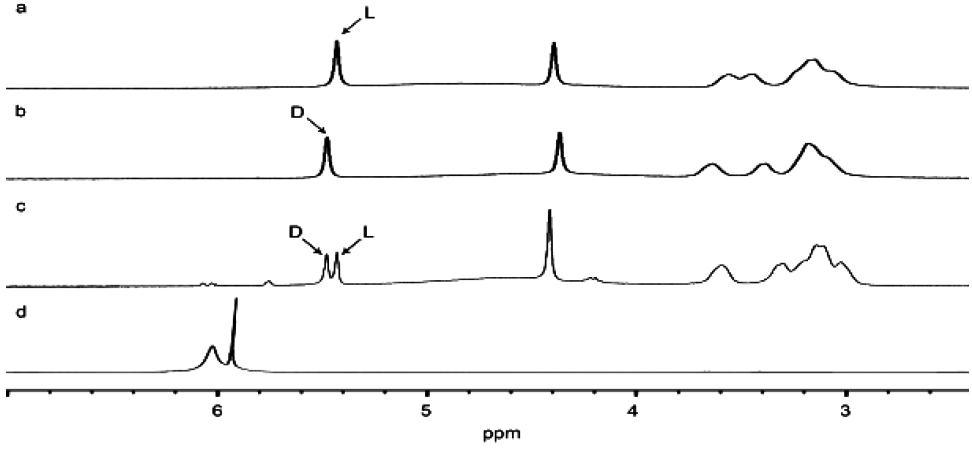


FIGURE 3 (a) Part of ^{1}H NMR of L-dibenzoyltartaric acid in the presence of compound **2**; (b) part of ^{1}H NMR of D-dibenzoyltartaric acid in the presence of an equimolar amount of compound **2**; (c) part of ^{1}H NMR of dibenzoyltartaric acid in the presence of an equimolar amount of compound **2**; (d) part of ^{1}H NMR of dibenzoyltartaric acid in the absence of host.

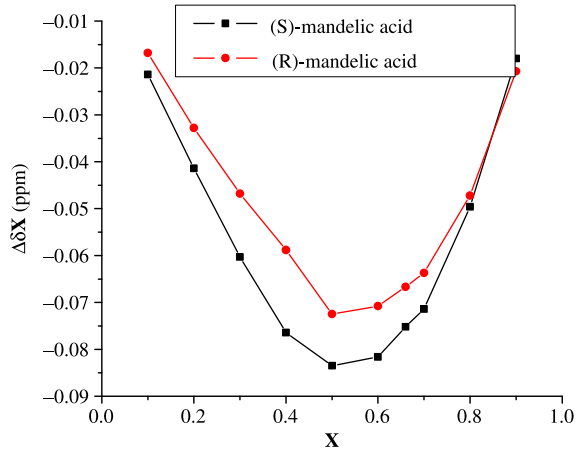


FIGURE 4 Job plots of compound **3** with (R)- and (S)-mandelic acids [X = molar fraction of the acid, Δδ = chemical shift change of the methine of (R)- and (S)-mandelic acids].

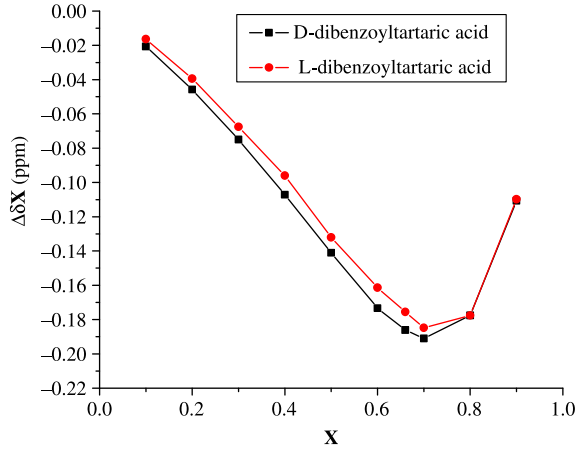


FIGURE 5 Job plots of compound 3 with (L)- and (D)-dibenzoyltartaric acids [X = molar fraction of the acid, Δδ = chemical shift change of the methine of (L)- and (D)-dibenzoyltartaric acids].

greater than those of (*R*)-mandelic acid in the presence of compound **3**.

Figure 5 shows the Job's plot of (D)-/(L)-dibenzoyltartaric acid with compound **3**. A minimum ΔδX was observed at X = 0.66, which indicated that the host **3** and (L)- or (D)-dibenzoyltartaric acid formed a 1:2 instantaneous complex. It was manifested that the chemical shift changes of (D)-dibenzoyltartaric acid were greater than those of (L)-dibenzoyltartaric acid in the presence of compound **3**.

In order to further study the complex abilities and the enantioselectivity of compound **3**, the titration curves of compound **3** with the enantiomers of mandelic acids or α-methoxyl-phenylacetic acid were plotted respectively (Figs. 6 and 7). It was found that the signals of the methine protons of (*R*)- and (*S*)-mandelic acids or (*R*)- and (*S*)-α-methoxy-phenylacetic acid in the ^{1}H NMR spectra continuously shifted upfield and reached a limiting value along with the concentration of compound **3** gradually increasing. We applied the non-linear least-squares fitting method on the ^{1}H NMR titration data [35,37–39] and obtained the association constants of each complex of compound **3** with the enantiomers of mandelic acids and α-methoxyl-phenylacetic acid (Table II). The results showed that the binding ability of compound **3** with R- enantiomers of mandelic acid and α-methoxy-phenylacetic acid was stronger than that with S- enantiomers of these guests and that the binding ability of compound **3** with mandelic acid was much stronger than that with α-methoxy-phenylacetic acid. This proved the foregoing conclusion that the α-hydroxyl group of the guest may play a crucial role for the stabilization of the host–guest instantaneous complexes.

We also tried to get the association constants of compound **3** with (L)- and (D)-dibenzoyltartaric acids, due to the poor solubility of the guest compounds in $CDCl_3$, the nonlinear least-squares fitting method could not be applied in this case.

CONCLUSION

In summary, three novel macrocyclic polyamides derived from L-/D-tartaric acid all exhibited certain chiral recognition ability towards the chiral carboxylic acids we had chosen. As a chiral solvating agent, the compound **3** has the excellent enantiomeric discriminating ability for mandelic acid and its derivatives, containing an α-OH at the chiral carbon, while the compound **2** has the best enantioselectivity towards dibenzoyltartaric acid. The results show that the magnetic anisotropy of the benzene ring in the compound **3** acts as an important factor in chiral recognition and the compounds **1** and **2**, which have less steric hindrance than compound **3**, more suitably fits dibenzoyltartaric acid. It is also proved

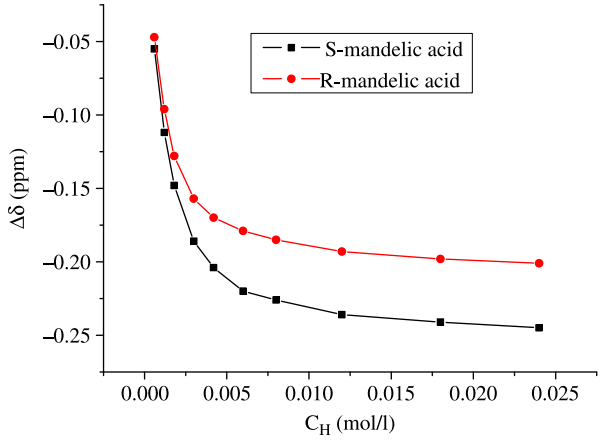


FIGURE 6 ^{1}H NMR titration curves of compound **3** with (R)- and (S)-mandelic acid.

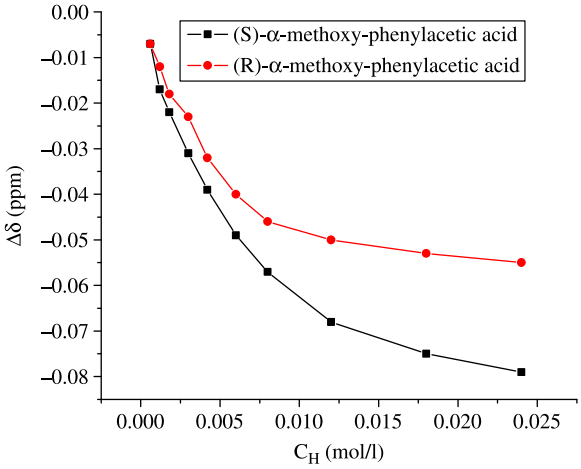


FIGURE 7 ^{1}H NMR titration curves of compound **3** with (R)- and (S)-α-methoxy-phenylacetic acid.

that the presence of α-hydroxyl or another carboxyl group in above guest molecules has stabilized the host–guest instantaneous complexes, therefore enhanced the enantioselectivity of the host molecules.

EXPERIMENTAL

Instruments and Material

^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Varian Mercury VX300 FT-NMR spectrometer (Varian, USA) with TMS (0.00 ppm) as internal reference operating at 298 K. Mass spectra (FAB) were recorded on a ZAB-3F-HF spectrometer. IR spectra were obtained on a Nicolet 170SX FT-IR spectrophotometer. Optical rotations were measured with a Perkin–Elmer Model 341LC polarimeter using the sodium D line at 589 nm. All melting points were uncorrected. Elemental analyses were determined on a Perkin–Elmer204B elemental auto analysis apparatus. Data collection for the crystal structure determination was carried out on the Bruker APEX2 CCD area detector using MoKα radiation (λ = 0.71073 Å) at a temperature of 273(2) K.

L-tartaric acid and cyclohexanone were purchased and directly used. Triethylenetetramine was commercially available and distilled before use. Reactions were carried out under an atmosphere of dry nitrogen, and the analytical solvents (cyclohexane, ethanol) were dried prior to being used. Diethyl L-tartrate and (2R, 3R)-1, 4-Dioxo-spiro[4.5]decane-2, 3-dicarboxylic acid diethyl ester were synthesized according to the lit [40–43].

TABLE II Association constants K_a $(mol/l)^{-1}$ of **3** with chiral carboxylic acids

Entry	Host	Guests	K_a $(mol/l)^{-1}$	$K_a(R)/K_a(S)$
1	**3**	(R)-mandelic acid	$(8.0 \pm 6.3) \times 10^3$	1.40
2	**3**	(S)-mandelic acid	$(5.7 \pm 3.2) \times 10^3$	
3	**3**	(R)-α-methoxy-phenylacetic acid	412 ± 46	1.63
4	**3**	(S)-α-methoxy-phenylacetic acid	253 ± 15	

(8R,21R)-7,22-dioxo-10,13,16,19-tetraaza-spiro[5.16]docosane-9,20-dione(2)

(2R,3R)-1,4-Dioxo-spiro[4.5]decane-2,3-dicarboxylic acid diethyl ester (8.59 g, 0.03 mol) was dissolved in absolute ethanol (200 ml) and then added to a solution of triethylenetetramine (0.03 mol) in 150 ml absolute ethanol, stirred at 40°C under nitrogen for 7 days, then the solvent was evaporated to dryness. The residue was chromatographed on alkaline alumina column (200 ~ 300 mesh, $CH_3OH/CHCl_3 = 3/97$ as eluant), to give the crude product, and then the product was crystallized in acetonitrile to afford a white solid. yield 15%, m.p. 198–200°C. $[\alpha]_D^{20} = +102.5°$ (c = 1.0, MeOH), ^{1}H NMR (300 MHz,$CDCl_3$): 6.85 (s, 2H, 2CON*H*), 4.41 (s, 2H, 2OC*H*), 3.68–3.64 (m, 2H, 2CONHC*H* H), 3.26–3.22 (m, 2H, 2CONHCH*H*), 2.86–2.81 (m, 2H, $CONHCH_2CH$ HNHCH$_2$), 2.73–2.65 (m, 6H, $CONHCH_2CHHNHCH_2$, $NHCH_2CH_2NH$), 1.80–1.41 (m, 12H, 2N*H*, C_6H_{10}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.344, 113.362, 78.490, 48.386, 47.879, 38.942, 35.810, 24.884, 23.706; MS(FAB): 341 $[M + 1]^+$; Anal. calcd. for $C_{16}H_{28}N_4O_4$: C, 56.45; N, 16.46; H, 8.29; Found: C, 56.27; N, 16.70; H, 8.05.

Measurements

^{1}H NMR Shift Experiments

Samples for analysis were prepared by mixing equimolar amounts of compounds **1**, **2** and **3** with the guest (the concentrations were normally 20 mM). The final volume was adjusted with $CDCl_3$ to 0.5 ml. The NMR tube was capped with a Teflon cap; its contents were mixed by inversion, allowed to stand for 10 min, and then placed in the spectrometer to obtain the ^{1}H NMR spectrum.

Determination of the Stoichiometry of Complexation

The stoichiometry of the host–guest complexes was determined by Job's method (the continuous variation method) [35–38]. The total concentration of the interacting species in the solution was kept constant at 3 mM and molar fraction of the host was varied in the range of 0.1–0.9.

^{1}H NMR Titration

The ^{1}H NMR titration experiments were performed as the following procedure, the guest compound was dissolved in an appropriate amount of solvent and the resulting solution evenly distributed among 11 NMR tubes. 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 $3.0{\cdot}10^{-3}$ M) were obtained: 0, 0.20, 0.40, 0.60, 1.00, 1.40, 2.00, 2.66, 4.00, 6.00, 8.00. The K_a values were calculated by a nonlinear least-squares fitting method for compound **3** from the observed $\Delta\delta$ values and the respective host and guest concentrations.

A representative example is given below: compound **3** versus (R)-α-methoxy-phenylacetic acid in $CDCl_3$. Weighed amounts: compound **3**: 48.01 mg in 1.00 ml; (R)-α-methoxy-phenylacetic acid: 2.74 mg in 3.30 ml. K_a(R) $[M^{-1}] = 412 \pm 46$.

Acknowledgements

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[34] Crystals suitable for X-ray analysis were obtained by recrystallization from acetonitrile at room temperature. Crystallographic data for the structure of compound **3** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-290467 These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal data of **3**: $C_{27}H_{36}N_4O_4$, $M = 480.60$, Monoclinic space group $P2(1)$, $a = 15.7369(18)$ Å, $b = 8.8210(10)$ Å, $c = 18.390(2)$ Å, $\beta = 90.652(2)^\circ$, $V = 2552.6(5)$ Å^3, $D = 1.251$ g/cm^3, $\mu = 0.085$ mm^{-1}, $F(0\ 0\ 0) = 1032$, $Z = 4$, $R_1 = 0.0429$, $\omega R_2 = 0.0630$. Data collection for the crystal structure determination was carried out on the Bruker APEX2 CCD area detector using MoKα radiation ($\lambda = 0.71073$ Å) at a temperature of 273(2) K. Of the 16671 reflections measured in the $2.22 \le \theta \le 27.49$ range, 10942 reflections were unique and 5389 reflections with $I > 2\sigma(I)$ were used in structure solution and refinement. $R_{int} = 0.0533$, calc $w = 1/[\sigma^2(F_o^2) + (0.0000P)^2 + 0.0000P]$, 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 leastsquares methods using anisotropic displacement parameters
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