*Journal of Inclusion Phenomena and Macrocyclic Chemistry* **43:** 87–93, 2002.
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# New Chiral Kemp's Acid Diamides for Chiral Amine Recognition by $^1$H NMR

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(Received: 11 September 2001; in final form: 12 February 2002)

*Key words:* chiral recognition, chiral Kemp's acid diamides, $^1$H NMR, titration, chiral shift reagent

**Abstract**

Two Kemp's acid diamides were synthesized and applied to chiral amine recognition using $^1$H NMR analysis. One derivative based on 1-(1-naphthyl)ethylamine had good chiral recognition of six amines and was useful to determine the optical purity for three amines, i.e., methylbenzylamine, 1-(1-naphthyl)ethylamine and 1-phenylpropylamine, however, the cyclohexylethylamine derivative showed little discrimination for the amines studied. Together with the results for alkylamines, it was shown that aromatic structure was important for aromatic shielding anisotropy and $\pi$–$\pi$ interactions between host and guest. The structure of the 1-(1-naphthyl)ethylamine derivative in solution was also considered based on $^1$H NMR data and computer simulation.

## Introduction

Recently, we reported that chiral Kemp's acid diamide **1** had good chiral recognition ability for some chiral amines [1] as a chiral solvating agent for NMR study [2–9]. In addition, **1** worked as a chiral shift reagent for *cis-N*-benzyl-2-aminocyclohexanemethanol [1]. Structural and/or conformational changes in the diastereomeric salt were expected to be the cause of chemical shift changes for both the acid and the amine. Even though **1** was expected to work as a resolving agent, unfortunately, due to low crystallinity of its chiral amine salts **1** was a poor resolving agent.

In order to understand the phenomena and improve usefulness, we studied the relationships between chiral recognition ability and structural features. For these purposes, we prepared new ligands **2** and **3** with increased size of the amide group of Kemp's acid diamide using naphthylethylamine and cyclohexylethylamine, and studied their $^1$H NMR titration behaviours. The property of Kemp's diacid monoamide **4** was also examined for monoamine, diamine, and hydroxylamine.

## Experimental

### *General*

$^1$H NMR spectra were measured on Bruker AC300P and ARX400 spectrometers. Infrared spectra were recorded on a JASCO FT/IR-400 spectrometer. Specific rotations were measured with a JASCO DIP-317 polarimeter.

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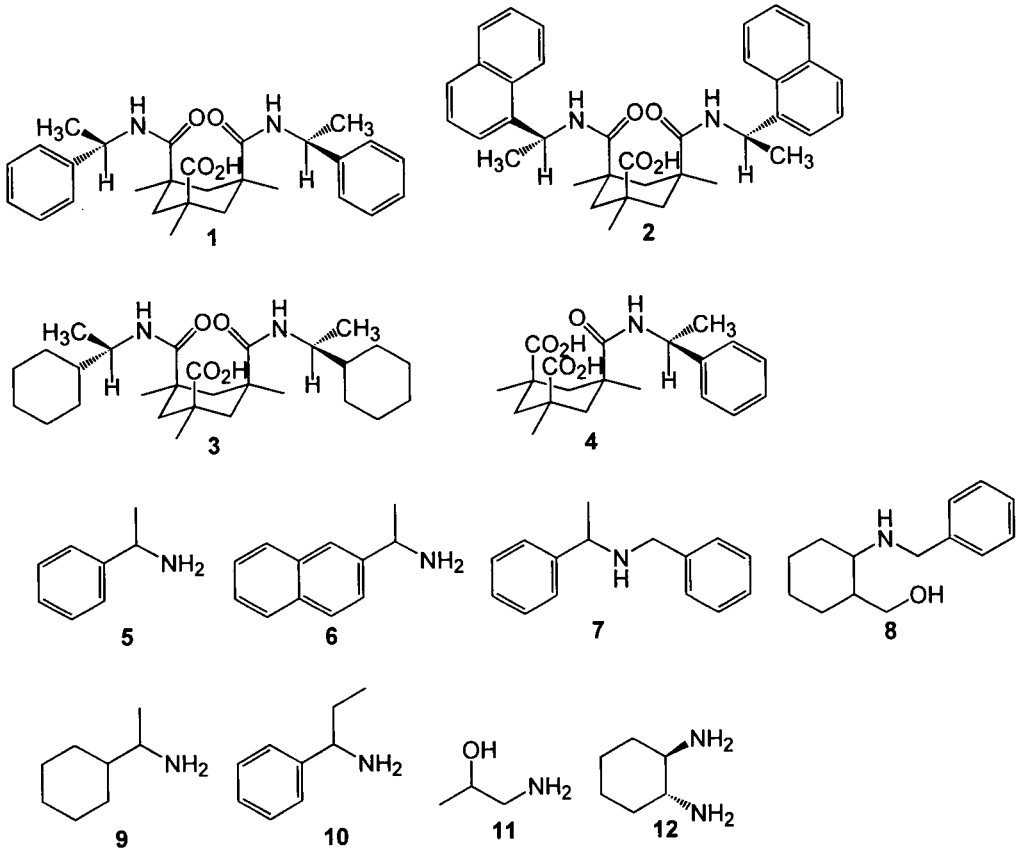
$\alpha$-Methylbenzylamine, 1-(1-naphthyl)ethylamine, *N*-benzylmethylbenzylamine, and $\alpha$-ethylbenzylamine were kindly supplied from Yamakawa Chemical Ind. Co., Ltd. 1-Cyclohexylethylamine, 1-amino-2-propanol, and *trans*-1,2-diaminocyclohexane were obtained from Aldrich Chemical Co. The analyte, *cis-N*-benzyl-2-aminocyclohexanemethanol, was prepared as in the literature [10].

### *cis,cis-1,3,5-Trimethyl-3,5-bis[(R)-1-(1-naphthyl)-ethylcarbamoyl]cyclohexane-1-carboxylic acid (**2**)*

According to the literature [1, 11] (*R*)-(+)-1-(1-naphthyl)ethylamine (197 mg, 1.15 mmol) was treated with the acid anhydride acid chloride of Kemp's triacid (138 mg, 0.53 mmol) in the presence of $Et_3N$ (121 mg, 1.20 mmol), and a catalytic amount of DMAP (4-dimethylaminopyridine) in dry THF (20 mL) for 20 h at rt. After removing the solvent under reduced pressure, the residue was dissolved in $CHCl_3$, washed with 1 mol/dm$^{-3}$ HCl aq., and dried over anhyd. $Na_2SO_4$. The solution was concentrated and the residue was purified by silica gel chromatography (EtOAc : hexane : $CH_3CO_2H$ = 40 : 60 : 1) to give a white solid after azeotropically removing $CH_3CO_2H$ by benzene (253 mg, 0.45 mmol, 83.9%); mp 113∼116 °C, $[\alpha]_D^{28}$ = 14.4 (*c* 1.0, EtOH), $^1$H NMR spectrum ($CDCl_3$) ppm: $\delta$ = 8.06 (d, *J* = 7.60 Hz, 2H), 7.86 (d, *J* = 7.92 Hz, 2H), 7.77 (d, *J* = 8.12 Hz, 2H), 7.50 (m, 8H), 7.35 (d, *J* = 4.77 Hz, 1H), 6.94 (d, *J* = 7.35, 1H), 5.91 (m, 2H), 3.00 (d, *J* = 16.53 Hz, 1H), 2.94 (d, *J* = 16.92 Hz, 1H), 2.72 (d, *J* = 15.45 Hz, 1H), 1.78 (d, *J* = 6.96 Hz, 3H), 1.70 (d, *J* = 6.96, 3H), 1.33 (s, 3H), ∼1.25 (1H), 1.18 (s, 3H), 1.13 (s, 3H), 1.05 (d, *J* = 15.06 Hz, 1H), 1.04 (d, *J* = 15.42 Hz, 1H); IR




*Scheme 1.*

(KBr) $cm^{-1}$: 3053, 3010, 2968, 2933, 1702, 1638, 1531. Found: C, 75.65; H, 7.48; N, 4.56. Calcd. for $C_{36}H_{40}N_2O_4$: C, 75.56; H, 7.14; N, 4.96.

*cis,cis-1,3,5-Trimethyl-3,5-bis[(S)-1-cyclohexyl-ethylcarbamoyl]cyclohexane-1-carboxylic acid (**3**)*

In the same way as described for **2**, (*S*)-(−)-1-cyclohexylethylamine (469 mg, 3.69 mmol) was reacted with the acid anhydride acid chloride of Kemp's triacid (463 mg, 1.78 mmol) in the presence of $Et_3N$ (377 mg, 3,73 mmol), and a catalytic amount of DMAP in dry THF (30 ml) for 22 h at rt. Following the treatment mentioned above, a white solid was obtained in 51.9% yield (441 mg, 0.93 mmol); mp 73∼75°C, $[\alpha]_D^{28} = -7.53$ (*c* 1.0, EtOH), $^1$H NMR spectrum ($CDCl_3$) ppm: $\delta$ = 6.88 (d, *J* = 8.46 Hz, 1H) 6.38 (d, *J* = 8.46, 1H), 3.77 (m, 2H), 2.96 (d, *J* = 15.08 Hz, 1H), 2.94 (d, *J* = 15.08 Hz, 1H), 2.72 (d, *J* = 15.81 Hz, 1H), 1.70 (m, 10H), 1.34 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.07 (d, *J* = 6.99 Hz, 3H), 1.02 (d, *J* = 6.99 Hz, 3H), 0.85∼1.20 (m, 15H); IR (KBr) $cm^{-1}$: 3018, 2930, 2855, 1712, 1633, 1542, 1450. Found: C, 70.70; H, 10.36; N, 5.58. Calcd. for $C_{36}H_{40}N_2O_4$: C, 70.55; H, 10.15; N, 5.88.

*c-5-[(S)-α-Methylbenzylcarbamoyl]-1,3,5-trimethyl-r-1, c-3-cyclohexanedicarboxylic acid (**4**)*

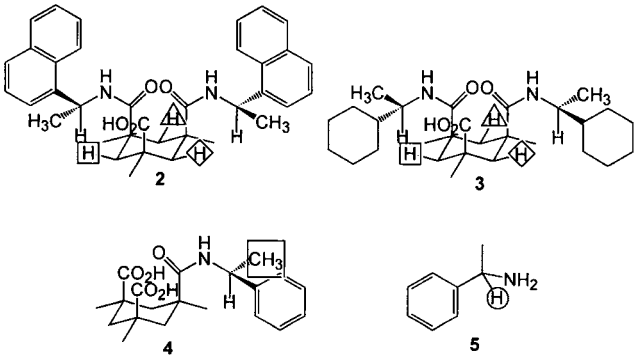
According to the literature [12], (*S*)-α-methylbenzylamine (179 mg, 1.48 mmol) was reacted with Kemp's acid 1,3-anhydride (338 mg, 1.41 mmol) in the presence of $Et_3N$ (287 mg, 2.84 mmol), and a catalytic amount of DMAP in dry THF (35 mL) for 20 h at rt. Following the treatment for **2** above, a white solid was obtained in 66.7% yield (339 mg, 0.94 mmol); mp 172∼174 °C, $[\alpha]_D^{28} = -29.5$ (*c* 1.0, EtOH), $^1$H NMR spectrum ($CDCl_3$) ppm: $\delta$ = 7.26 (m, 5H), 7.12 (1H), 4.85 (m, 1H), 2.86 (d, *J* = 15.1 Hz, 2H), 2.51 (d, *J* = 15.1 Hz, 1H), 1.42 (d, *J* =7.0 Hz, 3H), 1.26 (s, 3H), 1.20 (s, 2H), 1.02 (d, *J* =15.5 Hz, 2H), 0.97 (d, *J* = 15.5 Hz, 1H), Found: C, 66.56; H, 7.58; N, 3.85. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88.

*NMR measurement*

NMR titration was performed using a mixture of **2**, **3** or **4** ($1.0 \times 10^{-5}$ mol) and a certain amount of chiral amine or its racemate in $CDCl_3$ (500 $\mu$l) at rt. A standard pulse sequence was used for NOESY data collection and the spectrum of **2** was obtained using a mixing time, $\tau_m$, of 1.0 s [13].

*Calculations*

Simulation of the molecular structure of **2** by semi-empirical molecular orbital calculations was performed using MOPAC (PM3) on a SGI Power ONYX Computer in the Information Processing Center of Saitama University.




*Scheme 2.*

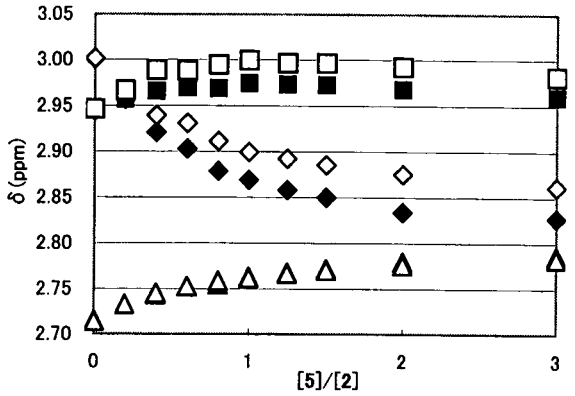



*Figure 1.* Chemical shift changes of equatorial protons of **2**. Filled symbols are the data of **2**+(*R*)-5. Open symbols are the data of **2**+(*S*)-**5**. See Scheme 2 for details of the symbols.

## Results and discussion

### *Chiral recognition ability of 2*

The chiral recognition ability of **2** was investigated for five chiral amines, **5–9**, by the $^1$H NMR titration method and the results of methylbenzylamine **5** are shown for some selected protons in Figures 1 and 2. As discussed in the previous paper [1], the chemical shift changes were probably caused by the salt formation between the carboxyl group of host **2** and the amino group of guest **5**, that is by "solvation" of the guest amine. Figure 1 shows the chemical shift changes of three equatorial protons on the cyclohexane ring of **2** as methylbenzylamine was added. In our previous study [1], two equatorial protons around 3 ppm were almost equivalent for **1**, but the corresponding signals for **2** shifted in opposite directions. The chemical shift change depended on the amount of **5**, approximately 0.1 ppm upfield-shift ($\Delta\delta$) was observed for a given proton at the 1 : 1 host-guest ratio. The chemical shift difference between (*R*)- and (*S*)-**5**, that is $\Delta\Delta\delta$, was obvious for these proton signals. Therefore it is clearly shown that **2** discriminates enantiomers of **5**. The situations were similar for other protons of **2** but to a lesser extent. On the other hand, Figure 2 shows the effect on the methine proton signals of **5** on its addition to **2**. The $\Delta\delta$ was very large (about 0.15 ppm downfield-shift) for (*S*)-**5**, but small for (*R*)-**5**.

Based on the $^1$H NMR titration data for **5–9** (Figures 1–3 and Supplementary), **2** was shown to work as a good

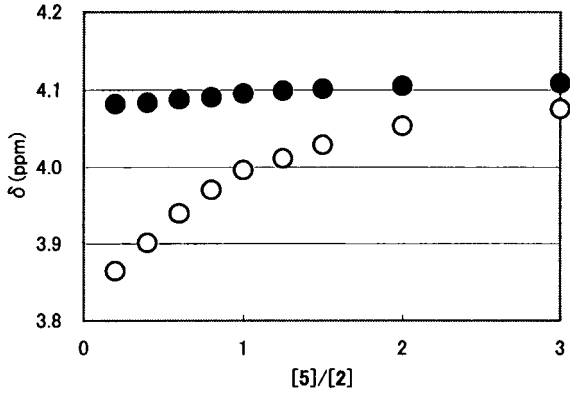



*Figure 2.* Chemical shift changes of methine protons of **5**. Filled symbols are the data of **2** + (*R*)-**5**. Open symbols are the data of **2** + (*S*)-**5**. See Scheme 2 for details of the symbols.

*Table 1.* Salt formation constants of **2** and **3** for five chiral amines **5–9** and the ratio between the diastereomer salts

| Chiral Kemp's diamide acid | Chiral Amine | | $K_a$ | $K_a(R)/K_a(S)$ |
|---|---|---|---|---|
| | **5** | *R* | 410 | 0.36 |
| | | *S* | 1150 | |
| | **6** | 1*S*,2*R* | 800 | 1.6 |
| | | 1*R*,2*S* | 500 | |
| **2** | **7** | *R* | 70 | 1.2 |
| | | *S* | 60 | |
| | **8** | *R* | 400 | 0.36 |
| | | *S* | 1100 | |
| | **9** | *R* | 1000 | 0.77 |
| | | *S* | 1300 | |
| | **5** | *R* | 90 | 1.8 |
| | | *S* | 50 | |
| | **6** | 1*S*,2*R* | 130 | 1.1 |
| | | 1*R*,2*S* | 120 | |
| **3** | **7** | *R* | 30 | 0.75 |
| | | *S* | 40 | |
| | **8** | *R* | 60 | 1.2 |
| | | *S* | 50 | |
| | **9** | *R* | 300 | 1.0 |
| | | *S* | 300 | |

chiral solvating agent. The salt formation constant $K_a$ was calculated using a nonlinear least-squares fitting method, summarized in Table 1. All $K_a$ values were determined using the methine protons of **2** and **3** except the systems of **3** : **7** and **3** : **8**, where amide protons of **3** were used due to unavailability of the methine proton signals. As seen in the table, some difference between $K_a(R)$ and $K_a(S)$ was observed as reported previously [1].

In addition, **2** was useful to determine the optical purities of **5** and **6** by $^1$H NMR measurements as shown in Figure 3 for the methine proton signals of both enantiomers of **5** and **6** at **2** : (*R*)-**5** : (*S*)-**5** = 1 : 0.4 : 0.4 and at **2** : (*R*)-**6** : (*S*)-**6** = 1 : 0.25 : 0.25 ratios, respectively. The host-guest ratio was determined considering $\Delta\Delta\delta$ between two enantiomers and overlapping of other signals, mostly those of

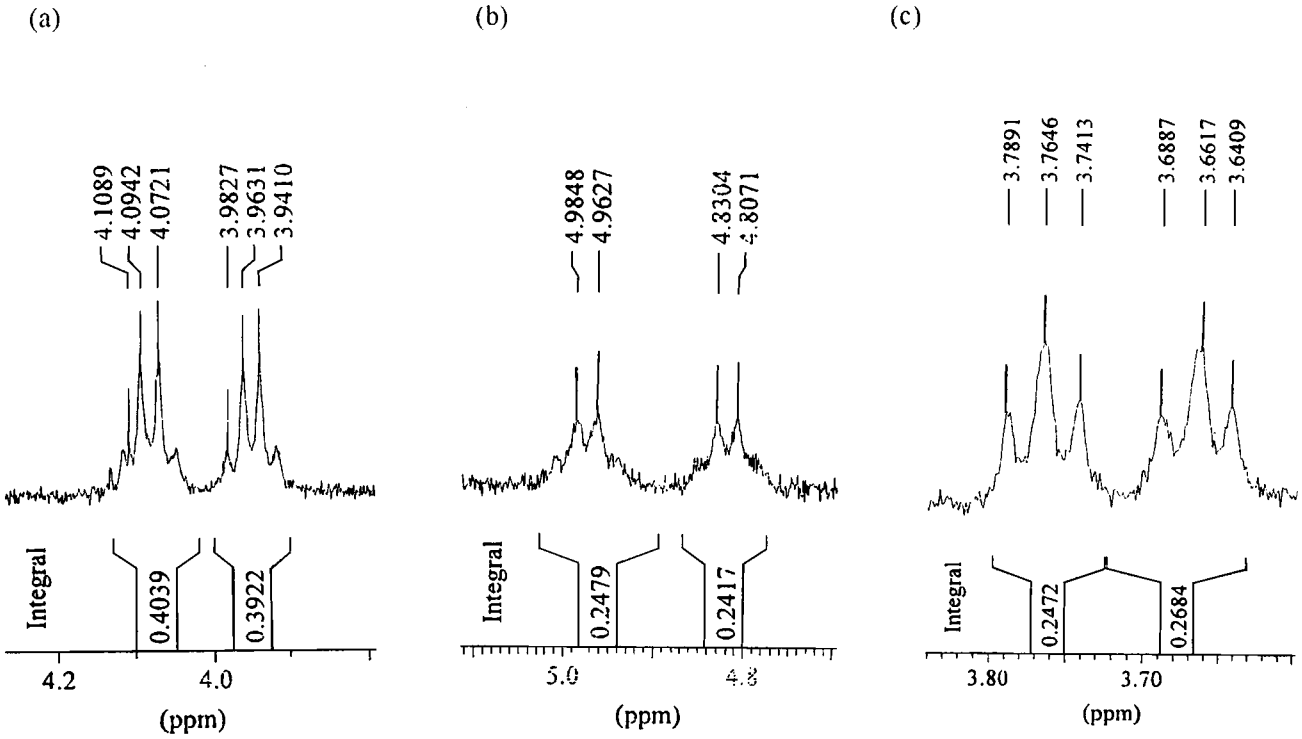



*Figure 3.* $^1$H NMR spectra of methine protons of **5** (a), **6** (b), and **10** (c). The host : guest ratios were as follows: (a) **2** : (*R*)-**5** : (*S*)-5 = 1 : 0.4 : 0.4, (b) **2** : (*R*)-**6** : (*S*)-**6** = 1 : 0.25 : 0.25, (c) **2** : (*R*)-**10** : (*S*)-**10** = 1 : 0.25 : 0.25.

ammonium protons, which shift greatly depending on the ratio of the guest amine to host. It was also found that the 1 : 0.5 mixture of **2** and racemic **10**, that is **2** : (*R*)-**10** : (*S*)-**10** = 1 : 0.25 : 0.25, gave enough separation of the methine protons of (*R*)- and (*S*)-**10** (Figure 3c). The signals at upper field in Figures 3a and 3b are those of (*S*)-**5** and (*S*)-**6**, respectively, as seen in Figure 2 for **5** (Supplementary for **6**). The same situation was expected for **10** considering the structural similarity with **5** and **6**; they are all $\alpha$-substituted benzylamine derivatives. In fact this expectation was proved true after the measurement of the 1 : 0.5 mixture of **2** and (*S*)-**10** giving the methine proton signal at ~3.6 ppm (data is not shown). Considering the results of **5**, **6**, **7** (Supplementary), and **10**, it is suggested that **2** causes larger upfield shifts for (*S*)-benzylic methine protons of chiral benzylamine derivatives.

*Chiral recognition ability of 3*

The other Kemp's acid diamide **3** was examined for interaction with **5–9** in the same way as **2** and partial results are shown in Figures 4 and 5 using **5** as an example. Figure 4 shows the data of three equatorial protons of **3** as in Figure 1 and the results seem similar to those of **2**, comparative $\Delta\delta$, but $\Delta\Delta\delta$ between two enantiomers is much smaller. As seen in Figure 5, the same result is obtained for the methine proton of **5**, much smaller $\Delta\Delta\delta$ than that observed in Figure 2 and the same tendency was obtained for **6–9** (Supplementary). As a result, $K_a(R)/K_a(S)$ for **3** became close to **1** as seen in Table 1. In addition the $K_a$ values were smaller for **3** than those for **2** and, therefore, **3** was concluded not to be useful for optical purity determination.

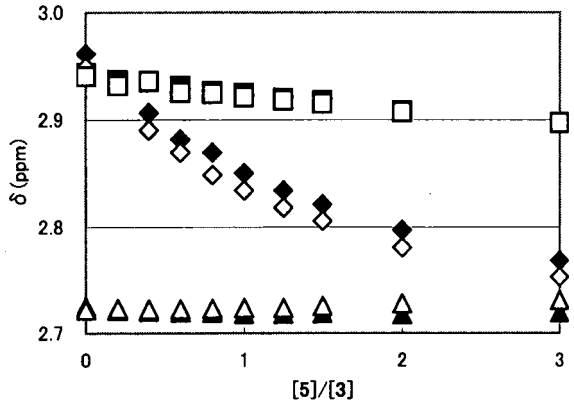



*Figure 4.* Chemical shift changes of methine protons of **3**. Filled symbols are the data of **3** + (*R*)-**5**. Open symbols are the data of **3** + (*S*)-**5**. See Scheme 2 for details of the symbols.

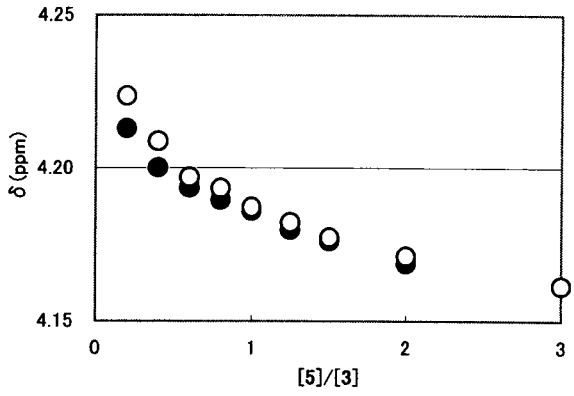



*Figure 5.* Chemical shift changes of methine protons of **5**. Filled symbols are the data of **3** + (*R*)-**5**. Open symbols are the data of **3** + (*S*)-**5**. See Scheme 2 for details of the symbols.

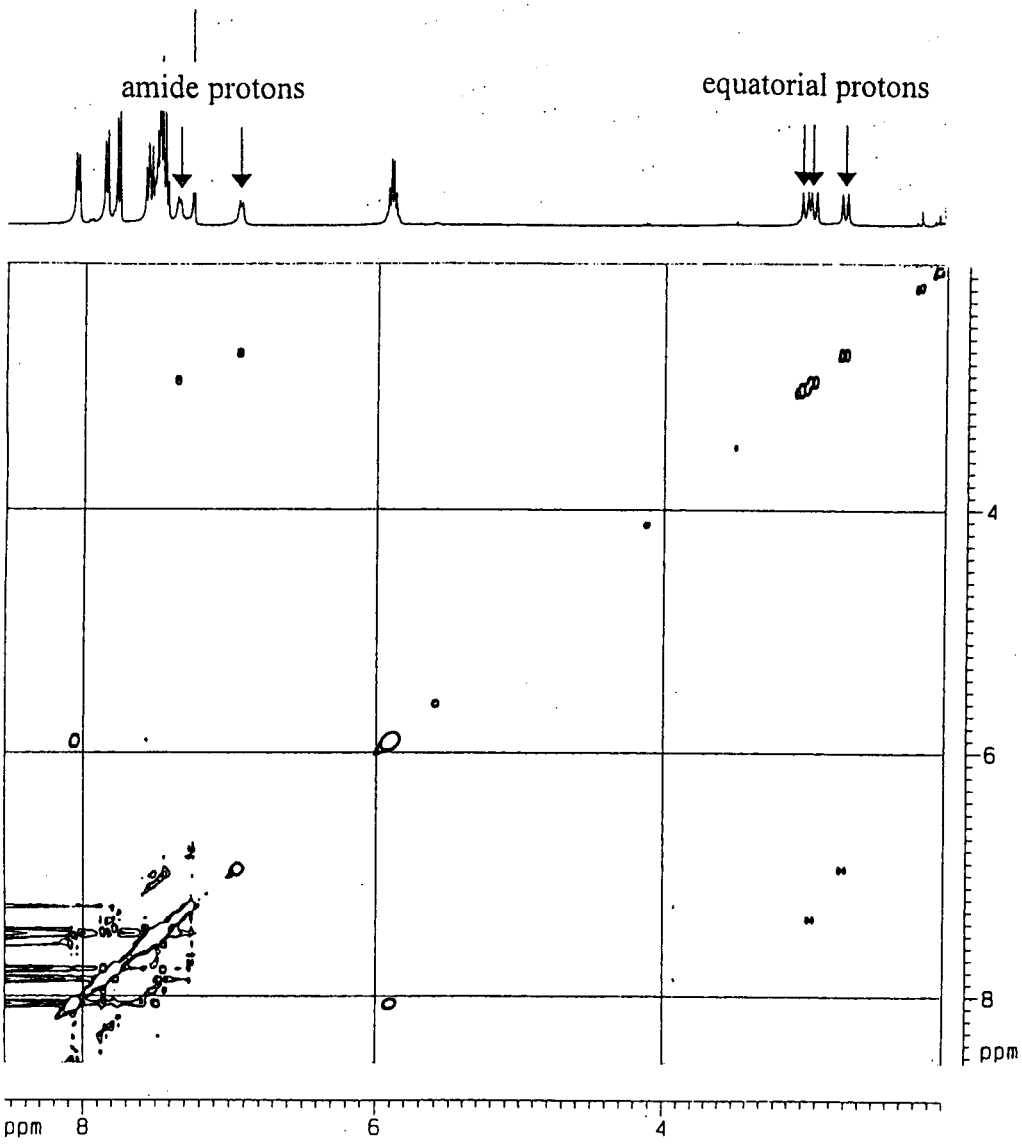



*Figure 6.* NOESY spectrum of **2** with $\tau_m$ = 1.0 s.

*Structural consideration*

The $^1$H NMR titration revealed that **3** gives only small or negligible $\Delta\Delta\delta$ between amine enantiomers studied, although a large $\Delta\delta$ is observed. Shifting our attention to amines, similar phenomenon, that is very small $\Delta\Delta\delta$ in spite of large $\Delta\delta$ was observed for the titration data of amine **9** with the acids **1** [1] and **2**. The results are consistent with the effects of the substituent on chiral recognition being different for cyclohexyl, phenyl or naphthyl groups. It appears clear that the bulky cyclohexyl group causes large structural changes, therefore $\Delta\delta$, by the acid-amine salt formation, which is the primary interaction between acid and amine. However it did not lead to discrimination of the enantiomers because the compounded steric bulk masked any subtle differences due to stereochemistry, as seen for chiral acid **3** and chiral amine **9**.

On the other hand, **1** and **2** have aromatic groups, which are able to cause the shielding anisotropy by phenyl or naphthyl groups and the anisotropy effect will lead to $\Delta\Delta\delta$ between amine enantiomers and will be larger for the more stable salt. The guest chiral amine having an aromatic group could have $\pi$–$\pi$ interaction with that of **1** and **2** as an additional binding force. As a result, stronger binding and therefore good discrimination was realized as seen for the cases of **5**, **6**, **7**, **8**, and **10**. In order to confirm this speculation, we also examined the chiral recognition of alkylamines such as 1-amino-2-propanol **11** for **1** and **2**. As expected almost no $\Delta\Delta\delta$ was observed between chiral and racemic amines, although a reasonably large $\Delta\delta$ was observed (Data not shown). Apparently, optimization of chiral discrimination requires aromatic character for both the guest amine and host Kemp's acid.

While **2** showed large $\Delta\delta$ and $\Delta\Delta\delta$ for **5**, **6** and **10**, **1** performed well only for **8** having an additional hydroxyl group [1]. Such additional functional groups seem to work better for chiral recognition due to multiple interactions with polar functional groups, like the amide group in the present case. However the titration data of **8** by **2** gave smaller $\Delta\Delta\delta$, $\sim$0.04 ppm for benzyl protons and $\sim$0.08 ppm for hydroxyl

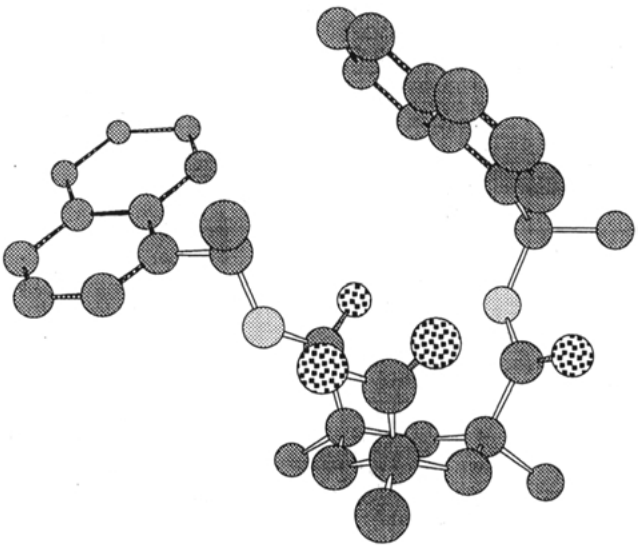


*Figure 7.* PM3 simulated structure of **2**.

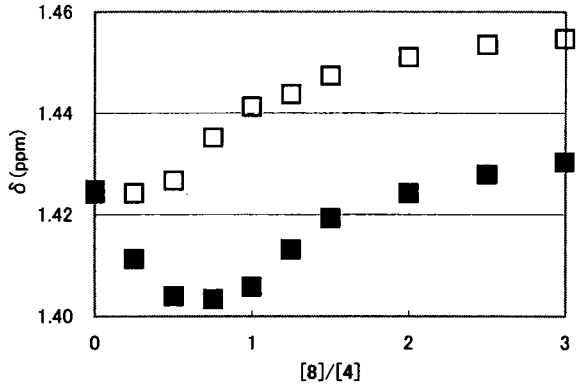



*Figure 8.* Chemical shift changes of methyl protons of **4**. Filled symbols are the data of **4** + (1*R*,2*S*)-**8**. Open symbols are the data of **4** + (1*S*,2*R*)-**8**. See Scheme 2 for details of the symbols.

methylene protons of **8** at the 1 : 1 ratio for **2** : **8** (Supplementary). Steric repulsion might be the reason but the cause of the different results between **1** and **2** needs to be further investigated.

As mentioned in the *Introduction*, the new acid diamides were designed expecting higher crystallinity of the amine salts due to increased hydrophobicity and/or greater interactions. However, unfortunately, none of the salts studied were crystalline. Chiral recognition ability is an important factor for resolution and great progress has been made in recent years [4–9]. Crystallinity or precipitation of a formed diastereomeric salt is also a very important feature for the diastereomer salt formation method, a typical and practical optical resolution method [14]. Further study is necessary to understand and control this property for development of effective resolving agents [15].

*Conformation of **2***

The $^1$H NMR spectrum of **2** revealed two amide proton signals and three equatorial proton signals. This resulted from the largely unsymmetrical structure of the acid diamide. In order to obtain conformational information in solution, the NOE was measured and the spectrum is shown in Figure 6. It was found that two amide protons have interactions with different equatorial protons. One amide proton at ~6.9 ppm interacts with one equatorial proton at ~2.7 ppm on the carbon atom between two carbon atoms having carbamoyl groups, and the other one at ~7.3 ppm with another equatorial proton at ~2.9 ppm. Based on the NMR information and the aid of a CPK molecular model study, we expect the conformation of **2** in $CDCl_3$ solution to resemble the structure in Figure 7. This experimentally determined structure corresponded to one of the possible conformations generated by PM3 molecular simulation. The simulation was supportive to understand the experimental data, although other conformations cannot be excluded considering the small differences of heat of formation, which is due to the flexibility of **2**.

Presently we interpret these results as follows: **2** forms an unsymmetrical but rather stable conformation in solution in the NMR time scale and either enantiomer of the guest amine is favourably chosen for salt formation; the effects of aromatic rings in the salt cause the chemical shift change difference. The bulky cyclohexyl groups of **3** should work for the unsymmetrical conformation. However the interaction of **3** with chiral amine becomes weaker due to lack of $\pi$-$\pi$ interaction, therefore the complex becomes less stable and much less $\Delta\Delta\delta$ is observed between diastereomeric salts.

*Chiral recognition ability of **4***

The discrimination ability of diacid **4** was investigated for chiral monoamines **5** and hydroxylamine **8** and diamine **12**. The $^1$H NMR data became complex as shown in Figure 8 for **8**. Presently the results can be explained by the stronger binding ability of **4**. Two carboxyl groups should work to bind amines more strongly than one. However stronger binding does not necessarily contribute to better chiral recognition nor to a uniquely stable structure. On the contrary, it might stabilize mismatched amine-acid salt structures as well. In addition, two carboxyl groups allow both 1 : 1 and 1 : 2 host : guest salt formation. The greater number of binding modes appears to cause complex titration results as seen in Figure 8. Similarly complex titration behaviour was observed for **5** and **12** (Supplementary).

## Conclusion

Two Kemp's acid diamides **2** and **3** were recently synthesized and their chiral recognition ability was studied for various amines using the $^1$H NMR titration method. While **2**, derived from 1-(1-naphthyl)ethylamine, had good chiral recognition ability for all amines studied and was useful to determine the optical purity for three $\alpha$-substituted benzylamines, **3**, derived from cyclohexylethylamine showed only small discrimination of enantiomers. Comparing with the results toward alkylamines, the effects of aromatic structure between host and guest, shielding anisotropy and $\pi$–$\pi$ interaction, was an important factor for differentiating

chiral amines. A preorganized highly chiral structure of **2** was expected from the $^1$H NMR data and PM3 computer simulation.

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