Revision of the Absolute Configurations of [8]Paracyclophane-10-carboxylic and 15-Methyl[10]paracyclophane-12-carboxylic Acids[1]

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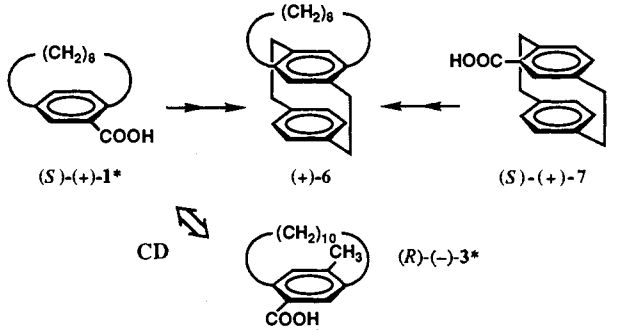
There have been two conflicting reports concerning the absolute configurations of [8]paracyclophane-10-carboxylic acid (**1**), [10]paracyclophane-12-carboxylic acid (**2**), and their derivatives. Schlogl et al. applied the empirical kinetic resolution method to [10]paracyclophane-12-carboxylic acid (**2**) and its derivatives to determine their absolute configurations.[2] Their conclusion was that acid (–)-**2** ($[\alpha]^{20}_D$ –80° ($CHCl_3$); CD λ_{ext} 297 ($\Delta\epsilon$ –0.78), 239 nm (–15.75)) had an *S* configuration. On the other hand, Nakazaki et al. reported the chemical correlation between (+)-[8]paracyclophane-10-carboxylic acid (**1**) ($[\alpha]^{18}_D$ +18.1° ($CHCl_3$); CD λ_{ext} 305 ($\Delta\epsilon$ +1.2), 248 nm (+15.1)) and (*S*)-(+)-[2.2]paracyclophane-4-carboxylic acid (**7**), by which they claimed that the absolute configuration of (+)-[8]paracyclophane-10-carboxylic acid (**1**) was *S* (Scheme I).[3] They also assigned an *R* configuration to (–)-15-methyl[10]paracyclophane-12-carboxylic acid (**3**) ($[\alpha]^{21}_D$ –28° (CH_3OH); CD λ_{ext} 294 ($\Delta\epsilon$ –1.3), 245 nm (–11.6)) because the CD spectrum of (–)-**3** was almost a mirror image to that of (*S*)-(+)-**1**.[3] However, it is quite strange that in spite of the similarity of the CD spectra including the sign between the two acids (*S*)-(–)-**2** and (*R*)-(–)-**3**, these acids have been assigned opposite absolute configurations each other. It implies that one of these results is erroneous.[4] One is based on the empirical kinetic resolution method, and the other is based on chemical correlation. Which determination is reliable and correct? Chemists have naturally believed that the latter assignment, based on the chemical correlation, was more reliable than the former.[3,5] However, we report here that the absolute configurations of [8]paracyclophane-10-carboxylic acid (**1**), 15-methyl-[10]paracyclophane-12-carboxylic acid (**3**), and their derivatives, which were chemically correlated to **1** and **3**, should be revised.

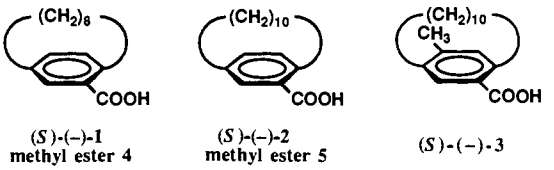
For the purpose of developing a new chiral stationary phase of HPLC, we prepared (–)-[10]paracyclophane-12-carboxylic acid (**2**) via optical resolution of diastereomeric amide derivatives **8** prepared with (*S*)-(–)-α-methylbenzylamine.[6] The diastereomer **8a** (mp 150–151 °C, $[\alpha]^{20}_{546}$ +6° (acetone)), obtained by fractional recrystallization from acetonitrile, was subjected to X-ray crystallographic structure analysis (Table I). The absolute stereochemistry of the carboxylic acid part was determined to be *S* by reference to the *S* absolute configuration of the chiral amine part, as shown in the ORTEP drawing of Figure 1. Since amide (+)-**8a** was converted to (–)-**2** ($[\alpha]^{20}_D$ –81.4° ($CHCl_3$)), the absolute configuration of (–)-**2** was determined to be *S*. This conclusion was in conflict with the chemical correlation and CD

Scheme I. Chemical Correlation of the Absolute Configurations of Cyclophanes[a]



[a] As reported by Nakazaki et al.[3] The absolute stereochemistry of compounds with * now should be reversed. However, the absolute configuration of compound **6** remains undetermined because it is not clear which chemical correlation is correct.

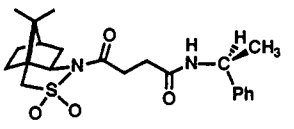
Chart I. Correct Absolute Stereochemistry of Chiral Cyclophanes



results reported by Nakazaki et al.[3] Therefore, we started to check the previously reported absolute configurations of the key compounds involved in the above controversy.

If the absolute configuration of [2.2]paracyclophane-4-carboxylic acid (**7**) is reversed, the conflict described above is solved. To directly confirm the previously assigned absolute configuration of acid **7**,[5,7] we carried out the X-ray crystallographic structure analysis of (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam amide derivatives, which unambiguously led to the *S* configuration of (+)-**7**.[8] Therefore, the absolute configuration of **7**, used as a reference compound in the chemical correlation described above, was correct.

If the absolute configuration of (–)-α-methylbenzylamine is reversed, the absolute configurations of (+)-**8a** and (–)-**2** are also reversed and are consistent with the chemical correlation results. We performed the X-ray analysis of a derivative (**9**) of (–)-α-methylbenzylamine,[9,10] but no error was found in the previous determination.[11]



(*S*)-**9**

The *S* configuration of (–)-**2** was established by the X-ray analysis of the camphorsultam amide derivative. The acid chloride of (±)-**2** was allowed to react with the anion of (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam generated with sodium hydride. The diastereomeric mixture of amides formed was separated by HPLC

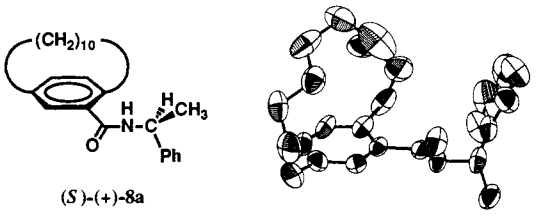
(1) Dedicated to the memory of Professor Gunther Snatzke (1928–1992).
(2) Eberhardt, H.; Schlogl, K. *Justus Liebigs Ann. Chem.* **1972**, *760*, 157 and references cited therein.
(3) Yamamoto, K.; Nakazaki, M. *Chem. Lett.* **1974**, 1051. Nakazaki, M.; Yamamoto, K.; Ito, M.; Tanaka, S. *J. Org. Chem.* **1977**, *42*, 3468 and references cited therein.
(4) Schwartz, L. H.; Bathija, B. L. *J. Am. Chem. Soc.* **1976**, *98*, 5344, note 4.
(5) Schlogl adopted the configurations of (*R*)-(–)-**1**, (*R*)-(+)-**2**, and (*R*)-(–)-**3**: Schlogl, K. *Top. Curr. Chem.* **1984**, *125*, 27. However, the combination of such configurations is self-inconsistent, as discussed in the text.
(6) Oi, S.; Miyano, S. *Chem. Lett.* **1992**, 987.
(7) The absolute configuration of [2.2]paracyclophane-4-methanol was determined by X-ray crystallography: Tochtermann, W.; Olsson, G.; Vogt, C.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1987**, *120*, 1523 and references cited therein.
(8) Harada, N.; Soutome, T.; Murai, S.; Uda, H. *Tetrahedron: Asymmetry*, in press. See also: Harada, N.; Hattori, T.; Suzuki, T.; Okamura, A.; Ono, H.; Miyano, S.; Uda, H. *Tetrahedron: Asymmetry*, in press.
(9) Harada, N.; Nehira, T., to be published.
(10) The previous X-ray studies of α-methylbenzylamine are for its salts.[11] Amide **9** is better than such salts for determination of the absolute configuration, because there is no chance to mistake a CH_3 group for an NH_3^+ group.
(11) Bush, M. A.; Dullforce, T. A.; Sim, G. A. *Chem. Commun.* **1969**, 1491 and references cited therein.

0002-7863/93/1515-7547$04.00/0

Table I. X-ray Crystallographic Data of Diastereomeric Amides (+)-**8a**, **10a**, and **11b**[a]

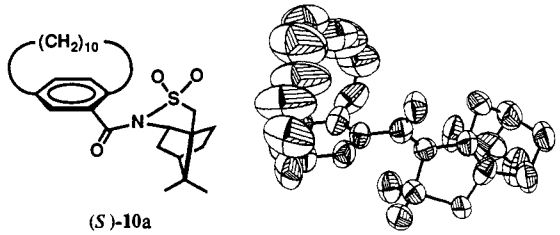
compound	(+)-8a	10a	11b
formula	$C_{25}H_{33}NO$	$C_{27}H_{39}NO_3S$	$C_{25}H_{35}NO_3S$
crystal system	orthorhombic	monoclinic	orthorhombic
space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a (Å)	9.8078 (5)	15.424 (2)	12.012 (1)
b (Å)	23.746 (2)	11.486 (1)	22.227 (2)
c (Å)	9.5357 (8)	14.780 (2)	8.6395 (4)
β (°)		90.75 (1)	
V (Å^3)	2220.8 (3)	2618.2 (5)	2306.6 (3)
Z	4	4	4
ρ(calcd) (g/cm^3)	1.087	1.159	1.237
ρ(obsd) (g/cm^3)[b]	1.087		
no. of indepdt reflcns $F_o > 3.0\sigma(F_o)$	1674	4019	2010
hydrogen, position	all, idealized	no	all, difference Fourier
absorption correction	face indices and size	no	statistical[c]
least-squares refinement	block diagonal	full matrix	full matrix
absolute configuration	S	S	S
final R (R_w)	0.0861	0.1119 (0.0750)	0.0441 (0.0457)
final R (R_w) for mirror image		0.1122 (0.0751)	0.0538 (0.0574)

[a] Rigaku AFC-6B automated four-circle diffractometer; Cu Kα (1.541 78 Å); monochromator, graphite crystal; temperature 20 °C; θ–2θ scan; 2θ scan limits, 2–130°; no indication of standard reflection decay during data collection. [b] By flotation using a CCl_4/hexane solution. [c] Katayama, C.; Sakabe, N.; Sakabe, K. *Acta Crystallogr.* **1972**, *A28*, 293.



(*S*)-(+)-**8a**

Figure 1. Absolute stereostructure and ORTEP drawing of (*S*)-(+)-**8a**.

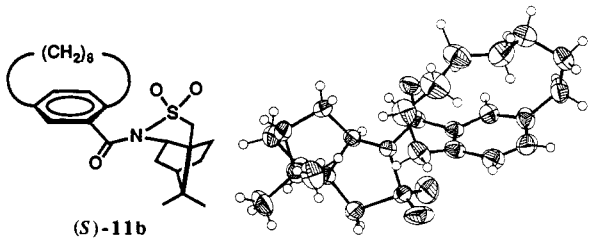


(*S*)-**10a**

Figure 2. Absolute stereostructure and ORTEP drawing of (*S*)-**10a**.

on silica gel (hexane/EtOAc 5:1). The solid material of the first eluted fraction was recrystallized from methanol to give plates, which were subjected to X-ray structure analysis: **10a**, mp 157–158 °C (Table I). The final R value remained large because of the disorder or large thermal vibration of the methylene bridge part and the existence of two molecules in one asymmetric unit, and therefore the absolute configuration could not be directly determined by the Bijvoet method. Instead, use of the (1*S*,-2*R*,4*R*)-2,10-camphorsultam part as an internal reference of absolute configuration definitely led to the *S* configuration of the acid part of **10a**, as shown in Figure 2. Amide **10a** was reduced with $LiAlH_4$ to give the alcohol, which was treated with Jones reagent and then with CH_2N_2 to yield methyl [10]paracyclophane-12-carboxylate ((–)-**5**) ($[\alpha]^{20}_D$ –55° ($CHCl_3$); CD λ_{ext} 299 ($\Delta\epsilon$ –0.8), 238 nm (–17.7)). The absolute stereochemistry of acid (–)-**2** and ester (–)-**5** was thus unambiguously determined to be *S*.

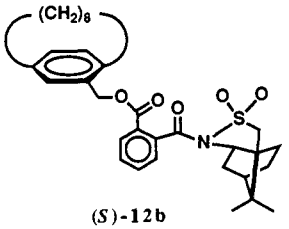
The absolute configuration of [8]paracyclophane-10-carboxylic acid was similarly determined by application of the camphorsultam method. A diastereomeric mixture of amides **11** prepared with (±)-**1** and (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam was separated by fractional recrystallization from methanol to yield one diastereomer (**11b**, mp 200–201 °C; CD λ_{ext} 261.0 ($\Delta\epsilon$ –9.7), 219.8 nm (+24.8)) as plates, which were subjected to X-ray analysis (Table I). The absolute configuration of **11b** was definitely determined to be *S* by the Bijvoet method, and also by the internal reference method, as shown in Figure 3. Amide **11b**



(*S*)-**11b**

Figure 3. Absolute stereostructure and ORTEP drawing of (*S*)-**11b**.

was also synthesized by another method: diastereomeric esters **12** prepared from (±)-[8]paracyclophane-10-methanol were separated by HPLC on silica gel (hexane/EtOAc 4:1). The ester



(*S*)-**12b**

12b of the second eluted fraction was converted, by hydrolysis and successive oxidation, to acid (*S*)-**1** (CD of methyl ester **4**, λ_{ext} 308 ($\Delta\epsilon$ –0.6), 247.2 (–15.7), 216.1 nm (+24.7)). Acid (*S*)-**1** was converted to a camphorsultam amide which was identical with **11b**.[12] The absolute stereochemistry of (–)-[8]paracyclophane-10-carboxylic acid (**1**) and its methyl ester **4** was thus determined to be *S*.

Since the absolute configurations of [8]paracyclophane-10-carboxylic acid (**1**) and 15-methyl[10]paracyclophane-12-carboxylic acid (**3**) are reversed, the absolute stereochemistry of [8][8]- and [8][10]paracyclophanes and other related compounds which were chemically correlated to acids **1** and **3** should be also revised.

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Supplementary Material Available: X-ray crystallographic structure analysis data of **8a**, **10a**, and **11b** (6 pages). Ordering information is given on any current masthead page.

(12) The other diastereomer (*R*)-**11a** of the camphorsultam amide was similarly prepared from the first eluted ester (*R*)-**12a**: CD of (*R*)-**11a**, λ_{ext} 300.0 ($\Delta\epsilon$ +1.2), 268.2 (–4.6), 244.5 (+9.1), 224.6 nm (–17.2). These diastereomers are easily distinguished by comparison of the CD data.