Communications to the Editor

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ASYMMETRIC REDUCTION OF ARYLGLYOXYLIC ACIDS VIA HOST-GUEST COMPLEX FORMATION WITH OPTICALLY ACTIVE PARACYCLOPHANES

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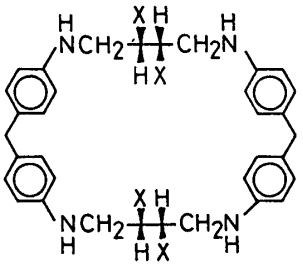
Reduction of 1-naphthylglyoxylic acid (**2c**) by inclusion complex formation with optically active paracyclophane (**1a**) followed by treatment with sodium borohydride in acidic water gave, after esterification with diazomethane, (R)-1-naphthylglycolic acid methyl ester (**4c**) in 9.7% ee. A working hypothesis is proposed to describe the mechanism of this reaction.

KEYWORDS ——— asymmetric reduction; paracyclophane; D_2-symmetry; host-guest complex; inclusion complex; arylglycolic acid; reaction mechanism; transition state

Water-soluble cyclophanes[1] constitute a group of hosts for organic guests to form 1:1 inclusion complexes in aqueous solution. In view of the importance of complementarity between hosts and guests to form complexes in particular geometries and with selectivities, these artificial hosts are of considerable interests because they have wide possibility of structural and functional modifications.

We have previously reported[2] the formation of diastereomeric inclusion complexes between chiral aromatic guests and an optically active paracyclophane (**1a**) in acidic water, as the first example of chiral recognition by complex formation with cyclophanes. We report here the asymmetric reduction of arylglyoxylic acids (**2a**, **2b**, **2c**) using optically active paracyclophanes (**1a**, **1b**[3]), as the first example of asymmetric reaction via inclusion complex formation with cyclophanes.[4]

The reactions were performed as shown in Chart 1. An important feature here is that the guests (**2**) should form inclusion complexes with optically active hosts (**1**) in the reduction step. In cases where **2b** and **2c** were used, no evidence for complex formation was observed when they were simply mixed with an acidic aqueous solution of the host, probably due to the low solubility of these guests in water. However, after ultrasonic vibration[5] of a mixture of finely powdered guest and an acidic aqueous solution of the host, the resulting supernatant was found to be a solution containing the objective inclusion complex.[6] The uncomplexed guest was left undissolved and was recovered.



1a : X = OCH_3
1b : X = $OCH_2CH_2OCH_3$

Reduction was carried out by adding sodium borohydride to this acidic aqueous solution,[8] and the product was isolated as the corresponding

Chart 1

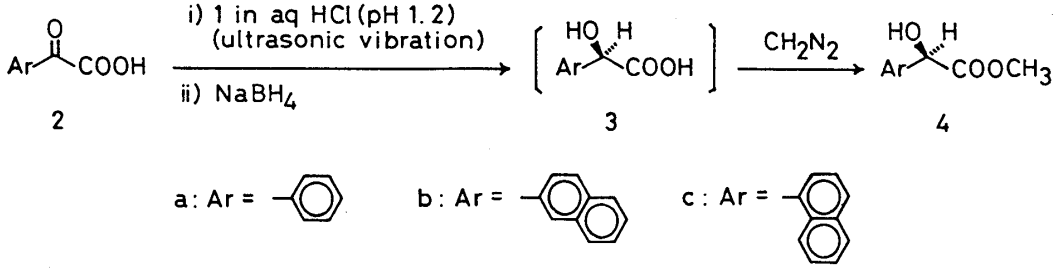


Table I. Asymmetric Reduction of Arylglyoxylic Acids[a)]

Entry	Host	Guest	Ultrasonic vibration (h)	Reduction time (h)	Product	Chemical yield (%)	ee (%)	Confign.
1	**1a**	**2a**	0[b)]	2	**4a**[c)]	53	2.4	R
2	**1a**	**2b**	6	3	**4b**[d)]	28(61)[e)]	3.9	R
3	**1a**	**2c**	4.5	3	**4c**[f)]	45(75)[e)]	9.7	R
4	**1b**	**2c**	4.5	3	**4c**[g)]	48(93)[e)]	7.0	R

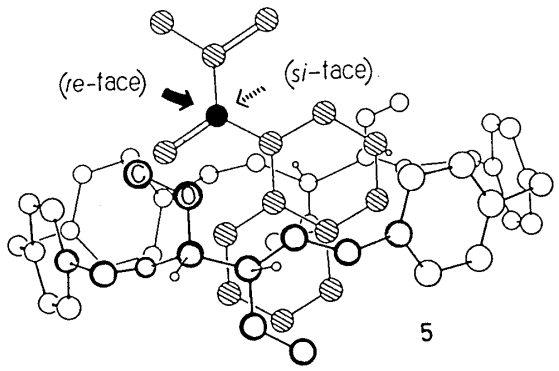
a) For procedure, see ref. 9. [**1**]=4x10^{-2}M and [**2**]=2x10^{-2}M before treatment with ultrasonic vibration. b) A clear solution was obtained without ultrasonic vibration. c) $[\alpha]_D^{21}$ -6.28°(c=1.08, CS_2). Reported $[\alpha]_D^{20}$ -253.1°(c=0.25, CS_2) for (R)-**4a**: P. Rona and R. Itelsohn-Schechter, Biochem. Z., 197, 428(1928). d) $[\alpha]_{435}^{20}$ -13.7°(c=2.67, $CHCl_3$). **3b** was resolved by the reported method: R. Howe, R. H. Moore, and B. S. Rao, J. Med. Chem., 16, 1020(1973). (S)-**3b** (63% ee) of $[\alpha]_D^{21}$ +89.8°(c=0.98, EtOH) thus obtained was converted to (S)-**4b** (63% ee) of $[\alpha]_{435}^{20}$ +222°(c=2.68, $CHCl_3$). e) Based on the unrecovered starting material. f) $[\alpha]_{435}^{16}$ -31.1°(c=1.68, acetone). Reported $[\alpha]_{435}^{16}$ +319°(c=1.5816, acetone) for (S)-**4c**: A. McKenzie and W. S. Dennler, Ber., 60, 220(1937). g) $[\alpha]_{435}^{16}$ -22.2°(c=1.59, acetone).

methyl ester (**4**)[9)](Table I).

The arylglycolic acid methyl esters (**4a**, **4b**, **4c**) obtained by using **1a** or **1b** as a host have the (R)-configuration in all cases. The highest ee (9.7%) was obtained by the combination of **1a** and **2c**.

From these data, we propose a working hypothesis to explain the mechanism of this asymmetric reduction as exemplified in **5**. It is reasonable to assume by our previous studies[1a)] that **1a** forms a complex with **2c** by accomodating the aromatic moiety of **2c** at its cavity. From CPK molecular model studies, it is expected that all methoxy groups of **1a** should be out of its cavity to provide room for the aromatic group. Anticipating steric hindrance between the two adjacent methoxy groups, the conformation of **1a** is assumed to be as shown in **5**, in which the methoxy groups are far apart from each other and are sticking up and down from the macrocyclic ring. In this conformation, **1a** has the D_2-symmetry and is not sided. Complexation of **2c** is expected to occur in a pseudo-axial manner[7)] as shown, and the attack of the reagent from the si-face is preferred to give (R)-**3** in excess, since the re-face is blocked by the methoxy group as shown.

It is previously shown[2)] that host-guest complexation using optically active paracyclophane can work in the ground state for the recognition of the chirality of



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the guest. Although ee values are low at present, it is now shown that these optically active paracyclophanes can also work in the transition state enantioselectively at the creation of chiral centers in the guests.

The present reduction process is intermolecular. An intracomplex version of this process may be more promising, and is a matter of future investigation.

REFERENCES AND NOTES

1) a) K. Odashima and K. Koga, "Cyclophanes," Vol II, ed. by P. M. Keehn and S. M. Rosenfeld, Academic Press, New York, 1983, Chapter 11; b) I. Tabushi and K. Yamamura, Topics in Current Chemistry, 113, ed. by F. Vögtle, Springer-Verlag, 1983, p. 145; c) Y. Murakami, ibid., 115, 1983, p. 107; d) F. Vögtle and W. M. Müller, Angew. Chem. Int. Ed. Engl., 23, 712(1984); e) F. Diederich and D. Griebel, J. Am. Chem. Soc., 106, 8037(1984); f) M. Daenens, L. Lacombe, J. M. Lehn, and J. P. Vigneron, J. Chem. Soc., Chem. Commun., 1984, 1097, and references cited.

2) I. Takahashi, K. Odashima, and K. Koga, Tetrahedron Lett., 25, 973(1984).

3) Prepared similarly as in the case of **1a**,[2] and characterized by elemental analysis (CHN) and spectral data (^{1}H-NMR, IR, Mass).

4) Asymmetric reactions via inclusion complex formation with cyclodextrins in aqueous solution are reported. For example, see M. Komiyama and M. L. Bender, "The Chemistry of Enzyme Action," ed. by M. I. Page, Elsevier, Amsterdam, 1984, Chapter 14.

5) We warmly thank Professor F. Vögtle, Bonn, for his valuable advice.

6) Evidence for 1:1 inclusion complex formation was obtained by ^{1}H-NMR spectra of this solution which was prepared by the same procedure using deuterated solvent (TMS (neat) as an external reference). Thus, signals of the protons of the guest are markedly shifted upfield compared to those in the absence of the host.[7] For example, under the condition of entry 3 of Table I, one of the proton signals of **2c** was shifted 1.6 ppm upfield.

7) Cf. K. Odashima, A. Itai, Y. Iitaka, Y. Arata, and K. Koga, Tetrahedron Lett., 21, 4347(1980).

8) The actual reducing agent is considered to be borane. Cf. H. C. Brown, "Borane in Organic Chemistry," Cornell Univ. Press, Ithaca, 1972.

9) The procedure (Entry 3, Table I) is as follows. Finely powdered **2c** (121.1 mg, 0.808 mmol) was added to a solution of **1a** (1.00 g, 1.60 mmol) in aq. HCl (pH 1.2, 40 ml) and the whole was subjected to ultrasonic vibration for 4.5 h. Undissolved **2c** (63 mg, 39%) was recovered. To the supernatant clear solution was added a solution of $NaBH_4$ (23.3 mg, 0.616 mmol) in H_2O (0.7 ml), and the whole was stirred at 0°C for 3 h. The acidic reaction mixture was extracted with AcOEt. The combined extracts were washed with satd. aq. NaCl, dried ($MgSO_4$), and evaporated to give crude **3c** (brown solid), which on treatment with excess diazomethane in MeOH-Et_2O followed by purification by column chromatography (silica gel, $CHCl_3$) gave **4c** (pale yellow solid, 78.4 mg, 75% yield based on the unrecovered **2c**).

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